The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper ~~153~~ 29

Filed by: Trial Division Merits Panel
Mail Stop Interference
P.O. Box 1450
Alexandria, VA 22313-1450
Tel: 571-272-9797
Fax: 571-273-0042

Filed
26 September 2005

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge James T. Moore)

RICHARD R. **BOTT**
and ANDREW SHAW,

Junior Party[1],
(Patent 5,763,385),

v.

ALLAN **SVENDSEN**,
HENRIK BISGARD-FRANTZEN, and TORBEN BORCHERT,

Senior Party[2],
(Application 09/327,563).

MAILED

SEP 26 2005

PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Patent Interference No. 105,206

Before: SCHAFER, MOORE, and NAGUMO, Administrative Patent Judges.

NAGUMO, Administrative Patent Judge.

DECISION – INTERLOCUTORY MOTIONS – BD.R. 125(b)[3]

---

[1] The real party in interest is identified as Genencor Int'l, Inc.

[2] The real party in interest is identified as Novozymes A/S, of Denmark.

[3] The terminology of the regulations currently in force, 37 CFR § 41.1 et seq. (effective 13 September 2004; see 69 Fed. Reg. 49960 (2004) will be used throughout this decision. The rules currently in force, 37 CFR § 41.1 et seq., will be followed except where either party has a reliance interest in the former

OUTLINE

Introduction

Findings of Fact
- The junior party
- The senior party
- The Count
- Claims of the parties
- Interlocutory motions
  - Bott motions
  - Svendsen motions
  - Additional briefing
- Bott disclosure
- Svendsen disclosure

The motions
- Construction of Bott's claims
  - Svendsen preliminary motion 4
  - Bott preliminary motion 8 and Svendsen preliminary motion 12
- Count 2
  - Bott preliminary motion 5
  - Bott preliminary motion 6
- Enablement
  - Bott preliminary motion 3
  - Svendsen preliminary motion 5
- Written Description
  - Bott preliminary motion 2
  - Svendsen preliminary motion 6
- Prior art motions
  - Bott preliminary motion 4
  - Svendsen preliminary motion 7
- Motions to add claims
  - Bott preliminary motion 7
  - Svendsen preliminary motion 13
- Reformation of the Count
- Motion for benefit
- Miscellaneous motions

Order

---

rules. *Singh v. Brake*, 222 F.3d 1362, 1371, 55 USPQ2d 1673, 1679 (Fed. Cir. 2000) (In the absence of a reliance interest, the current law is applied.)

I. Introduction

This interference concerns modified or variant enzymes (proteins) called α-amylases that break down certain starches into smaller molecules. The inventive α-amylases are said to be useful in a variety of industrial processes because they are, for example, more stable at high temperatures or high pH (alkaline conditions) than the native enzymes. Moreover, the inventive α-amylases are said to not require high concentrations of calcium ions (Ca^{2+}) for stability, permitting the formulation of cheaper detergent compositions.

An oral hearing was conducted before a court reporter on 8 March 2005.[4] Steven B. Kelber, Esq., accompanied by Dr. Sue Jensen, M.D., appeared on behalf of Bott. John T. Callahan, Esq., accompanied by Kenneth J. Burchfiel, Esq., and Timothy Miegs, Esq., appeared on behalf of Svendsen.

The panel ruled from the bench that Svendsen preliminary motion 4, for judgment that Bott's involved claims are indefinite, was DENIED. (Paper 150 at 5.) The reasons are set out *infra*. Under the original Count 1, Bott maintained in preliminary motion 5 that there was no interfering subject matter between any of Svendsen claims 192+ and any of Bott's claims, and

---

[4] Transcript, Paper 150.

in preliminary motion 6 that claim 192 should be designated as not corresponding to Count 1. Under Count 2, Svendsen claim 192 forms an alternative definition of the count. Bott's original preliminary motion 6, to designate Svendsen claim 192 as not corresponding to Count 1, was retained as a motion to reformulate Count 2 as excluding Svendsen claim 192. (Paper 139 at 2.) We have elected to take up Bott preliminary motion 5, that there is no interference in fact between any of Bott's claims and any of Svendsen claims numbered 192 and higher, as a motion to reform Count 2. Bott preliminary motion 5 is DENIED. As a result of the decisions on the motions, all of Bott's claims and all but Svendsen claim 192 have been held not patentable to the respective parties. We have considered whether the addition of a reissue application filed by Bott that has not been examined would assist the resolution of priority in this interference. In light of our decisions on preliminary motions, however, none of the claims proposed by Bott in the reissue application are patentable to Bott. Accordingly, Bott preliminary motion 7 is DENIED. Svendsen preliminary motion 13, to add claims to Svendsen's pending application, has been GRANTED. The interference is redeclared according to Count 3 in a separate order accompanying this decision. See Paper 154.

II. Findings of Fact

The following findings of fact, and those set out in the discussions, are supported by a preponderance of evidence in the record.

The junior party

1. Bott is involved on the basis of U.S. Patent No. 5,763,385 (BX 2003[5], "385 patent"), which is titled "Modified alpha-amylases having altered calcium binding properties."

2. The inventors of the 385 patent are said to be Richard R. Bott and Andrew Shaw.

3. The 385 patent is based on original application 08/645,971, filed 14 May 1996.

4. No claim for the benefit of any earlier application appears in the record of the 385 patent.

5. The real party in interest for Bott is said to be Genencor International, Inc.

The senior party

6. Svendsen is involved on the basis of application 09/327,563 (SX 1007, the "563 application"), filed 8 June 1999, titled "Alpha-amylase mutants."

7. The 563 application claims the benefit under 35 U.S.C.

---

[5] Bott exhibits are cited as BX 2___; Svendsen exhibits are cited as SX 1___.

§ 120 of the following applications, as being:

a continuation of 08/683,838 (SX 1006, the "838 application"), filed 18 July 1996, now U.S. Patent No. 6,022,724, which is said to be:

a continuation-in-part of 08/600,908 (SX 1005, the "908 application"), filed 13 February 1996, now U.S. Patent No. 5,989,169, which is said to be:

a continuation of international application PCT/DK96/00057 (SX 1004, "PCT application"), which was filed on 5 February 1996.

8. The PCT application was published as WO96/23874 on 8 August 1996. (SX 1004 at 1.)

9. The 563 application claims the benefit under 35 U.S.C. § 119 of the following foreign applications:

Denmark 0128/95, filed 3 February 1995 (SX 1001);

Denmark 1192/95, filed 23 October 1995 (SX 1002);

Denmark 1256/95, filed 10 November 1995 (SX 1003).

10. Svendsen has been accorded the benefit for priority of the 838 and the 908 applications, and has been designated the senior party in this interference. (Paper 1 at 4.)

11. The real party in interest for Svendsen is said to be Novozymes, A/S, of Denmark.

The Count

12. This interference was redeclared on 19 January 2005. (Paper 121.)

13. The sole count in the interference is now Count 2, which reads:

> A composition of matter in accordance with any one of claims 77-81, 84-88, 90-92, 97, 113 and [sic: or] 192 of Svendsen application 09/327,563
>
> or
>
> a composition of matter in accordance with any one of claims 1 or 9-28 of Bott patent 5,763,385.

14. Claim 113 of Svendsen reads (underscore added):

> An alpha amylase comprising an A domain, a C domain and a calcium binding site, wherein said calcium binding site is associated with said A domain and said C domain and comprises ligand residues in said A domain and/or said C domain, wherein said alpha amylase is modified to alter the characteristics of said calcium binding site and thereby alter the performance of said alpha amylase by substituting an amino acid residue at a position corresponding to one or more of Q298, G299, G301, Y302, L307, F343, F403, H405, H406, D407, L427, I428, D430, and G475 in Bacillus licheniformis (SEQ ID NO:2).

15. Claims 77-81, 84-88, 90-92, and 97 of Svendsen differ from claim 113 of Svendsen in that each claim specifies a single amino acid residue, selected from the list recited in claim 113, that is to be substituted by another amino acid residue.

16. Claim 192 of Svendsen reads:

> A variant of a parent α-amylase, said parent alpha-amylase having SEQ ID NO. 2, in which variant the amino acid residues 325-345 of the parent α-amylase have been replaced with amino acid residues 294-313 of SEQ ID No. 10.

17. Bott claim 1 reads:

> An α-amylase comprising an A domain, a C domain and a calcium binding site, wherein said calcium binding site is associated with said A domain and said C domain comprises ligand residues in said A domain and/or said C domain, wherein said α-amylase is modified to alter the characteristics of said calcium binding site and thereby alter the performance of said α-amylase by substituting an amino acid residue at a position corresponding to one or more of, Q298, G299, G301, Y302, L307, N309, Q340, F343, F403, H405, H406, D407,, G410, L427, I428, D430, G433, K436, N473, G474 and G475 in *Bacillus licheniformis*.

18. Bott claims 9-28 differ from Bott claim 1 in that they each specify the amino acid residue, selected from the list recited in Bott claim 1, that is to be substituted by another amino acid residue.

19. Certain Bott claims further contain a single-letter typographical error.

20. The text of Svendsen claim 113 differs from that of Bott claim 1 in that Svendsen's claim recites the underscored "and," and the term "SEQ ID NO:2," and does not recite certain residues (N309, Q340, G410, G433, K436, N473, and G474).

Claims of the parties

21. In the course of redeclaring the interference, a merits panel of the Board of Patent Appeals and Interferences ("Board") has determined that Svendsen is not entitled to a patent containing claims 193, 197, 202, 205, and 209–213. (Paper 121 at 13.)

22. Svendsen has not sought reconsideration of the Board's patentability determination regarding Svendsen claims 193, 197, 202, 205, and 209–213.

23. The claims of the parties are:

Bott: 1-28

Svendsen: 77-81, 84-88, 97, 113-118, 120, 192, 194-196, 198-201, 203, 204, 206, and 208.

24. The claims of the parties that correspond to Count 2 and therefore are involved in the interference are:

Bott: 1-28

Svendsen: 77-81, 84-88, 97, 113-118, 120, 192, 194-196, 198-201, 203, 204, 206, and 208.

25. The claims of the parties that do not correspond to Count 2 and therefore are **not** involved in the interference are:

Bott: none

Svendsen: none.

26. In the redeclaration, the Board also ordered "that

Svendsen Preliminary Motion 10 is dismissed to the extent that it seeks to amend or add claims, all without prejudice to Svendsen filing . . . a paper which (1) selects no more than five (5) claims for consideration and (2) explains why the five claims are being presented." (Paper 121 at 13.)

27. Svendsen timely filed such a paper (styled Svendsen Preliminary Motion 13 (Paper 128), in which Svendsen presented five new claims to add to its specification.

28. Bott was not authorized to file oppositions to any paper filed by Svendsen in response to the redeclaration order. (Paper 121 at 13.)

Interlocutory motions

The following motions are before the Board for decision.

Bott motions[6]

29. Bott Preliminary Motion 2, for judgment that all Svendsen claims, other than claim 192, lack adequate written description. (Paper 43; Opposition 2, Paper 70; Reply 2, Paper 107.)

30. Bott Preliminary Motion 3, for judgment that all Svendsen claims lack an enabling disclosure. (Paper 42; Opposition 3, Paper 71; Reply 3, Paper 108.)

---

[6] Bott Preliminary Motion 1 (Paper 18) has been withdrawn (Paper 44).

31. Bott Preliminary Motion 4, for judgment that Svendsen claims 192-206 and 208-213 are unpatentable over prior art. (Paper 41; Opposition 4, Paper 72; Reply 4, Paper 109.)

32. Bott Preliminary Motion 5, for judgment that there is no-interference-in-fact between Bott claims 1-28 and Svendsen claims 192-206 and 208-213. (Paper 40; Opposition 5, Paper 73; Reply, Paper 110.) This motion will be considered as part of a request for reconsideration of the redeclaration of the interfering subject matter according to Count 2. (Cf. Paper 139 at 2.)

33. Bott Preliminary Motion 6, to designate Svendsen claim 192 as not corresponding to Count 1. (Paper 39; Opposition 6, Paper 74; Reply 6, Paper 111.)

34. Bott Preliminary Motion 7, to add a reissue application that corrects alleged typographical errors and that adds certain dependent claims. (Paper 38; Opposition 7, Paper 75; Reply 7, Paper 112.)

35. Bott Preliminary Motion 8, to correct alleged typographical errors in Count 1. (Paper 58; Opposition 8, Paper 76; Reply 8, Paper 113.)

36. Bott has filed a motion to suppress testimony by Herzberg (SX 1046), on which Svendsen relies in SVENDSEN preliminary motion 14. (Paper 126; Opposition, Paper 135; Reply,

Paper 143; Observations on cross examination, Paper 125; Response to observations, Paper 134.)

Svendsen motions

37. As a result of the redeclaration of this interference according to Count 2 (Paper 121) and subsequent related requests, Svendsen has withdrawn Svendsen Preliminary Motions 1-3, 8, and 9 (see Papers 129 and 133.)

38. Svendsen Preliminary Motions 4-7, and 11-14 are before the Board for consideration. (See Papers 121 and 130.)

39. Svendsen Preliminary Motion 4, for judgment that all Bott claims are indefinite. (Paper 31; Opposition 4, Paper 81; Reply 4, Paper 96.)

40. Svendsen Preliminary Motion 5, for judgment that all Bott claims, but for Bott claim 3, lack an enabling disclosure. (Paper 32; Opposition 5, Paper 82; Reply 5, Paper 97.)

41. Svendsen Preliminary Motion 6, for judgment that all Bott claims, but for Bott claim 3, lack an adequate written description. (Paper 33; Opposition 6, Paper 83; Reply 6, Paper 98.)

42. Svendsen Preliminary Motion 7, for judgment that Bott claims 1-7, 14, 18, 22, and 25 are unpatentable over prior art. (Paper 34; Opposition 7, Paper 84; Reply 7, Paper 99.)

43. Svendsen Preliminary Motion 11, contingent on the grant of Bott Preliminary Motion 7 to add Bott's reissue application, seeks to require Bott to add claims 36-46, said to correspond to Count 1. (Paper 57; Opposition, Paper 88; Reply, Paper 101.)

44. Svendsen Preliminary Motion 12, contingent of the grant of Bott Preliminary motion 8, to correct the count, seeks the benefit for priority with respect to the corrected count, of Svendsen's foreign priority, PCT, and parent United States applications. (Paper 91; Opposition, Paper 114; Reply, Paper 119.)

45. Svendsen Preliminary Motion 13, to add new claims 214-218 to the involved 563 application. (Paper 128.) Bott was not authorized to file an opposition to this motion. (Paper 121 at 13.)

46. Svendsen Preliminary Motion 14, seeks the benefit for priority with respect to Count 2, as established in Paper 121, of Svendsen's foreign priority, PCT, and parent United States applications. (Paper 132; Opposition, Paper 142; Reply, Paper 145.)

47. Svendsen filed a miscellaneous motion to file a Certificate of Correction under 35 U.S.C. § 254 to correct the notification of priority claim in Patent 6,022,724, which issued from the parent application of Svendsen's involved 563

application. (Paper 35.)

48. Svendsen filed a miscellaneous motion to suppress evidence relied on by Bott in Bott Oppositions 5 and 6. (Paper 123.)

Additional briefing

49. In response to an invitation by the Board (Paper 92), Bott and Svendsen each filed Briefs regarding:

(a) The proper scope of the Count (Bott, Paper 117; Svendsen, Paper 103);

(b) the validity of Bott's involved claims over WO94/14954 (Bott, Paper 116; Svendsen, Paper 105); and

(c) the patentability of Svendsen's involved claims over prior art (Bott, Paper 115; Svendsen, Paper 105).

As will be seen, we need not consider these briefs.

The following summaries of the Bott and Svendsen specifications introduce the subject matter of the interference in detail.

Bott disclosure relating to terms in Bott claim 1 and the Count

α-amylase

50. According to Bott's 385 patent, "α-Amylases (α-1,4-glucan-4-glucanohydrolase, EC3.2.1.1) hydrolyze internal α-1,4-glucosidic linkages in starch, largely at random, to produce

smaller molecular weight malto-dextrins." (BX 2003 at col. 1, ll. 16-19.)

51. More specifically, Bott defines the term "α-amylase" as follows: "'α-amylase' means any enzymatic activity which cleaves or hydrolyzes the α(1-4) glycosidic bond, e.g., that [bond] in starch, amylopectin or amylose polymers. α-Amylase as used herein includes naturally occurring α-amylases as well as recombinant α-amylases." (BX 2003 at col. 5, ll. 39-45.)

52. Bott displays a representation of the structure of α-amylase from the bacterium *Bacillus licheniformis* in Figures 1 and 2 of the 385 patent (BX 2003.) These figures appear to be derived from the crystal structure described in example 1 (BX 2003 at cols. 13-14).

53. According to Bott, "the first three residues of the N-terminus and the C-terminal residue are missing. Also missing are residues **181-195** of molecule 1, and **181-193** of molecule **2**." (BX 2003 at col. 14, ll. 41-44, emphasis original.)

54. Although Bott provides the amino acid sequence of the mature α-amylase from *Bacillus licheniformis* (BX 2003, figure 4, and in SEQ ID NO:2, at cols. 17-20), and an alignment of that sequence with the corresponding sequences of α-amylase from *Bacillis amyloliquefaciens* and from *Bacillus stearothermophilus*

(BX 2003 at figure 5), Bott does not provide coordinates for the x-ray structure.

A and C domains

55. Bott teaches that "[t]hree dimensional structure similarities between various α-amylases (and related amylolytic enzymes like cyclodextrin gl[u]cosyltransferases and α-glucosidases) from different organisms, despite common differences in their primary structures, are found in the common presence of an α/β-barrel forming a central part (domain A), a Greek key motif as a separate domain C and at least one additional domain, domain B." (BX 2003 at col. 3, ll. 10-20, citing Machius[7], BX 2005.)

calcium binding site

56. In Bott's words,

> [a]ccording to the present invention, an α-amylase is provided comprising an A domain, a C domain and a calcium binding site, wherein the calcium binding site is associated with the A domain and the C domain and comprises ligand residues in the A domain and/or the C domain, wherein the α-amylase is modified to alter the characteristics of the calcium binding site and thereby alter the performance of the α-amylase.

(BX 2003 at col. 4, ll. 8-15; cf. col. 7, ll. 1-8 for substantively the same wording.)

---

[7] M. Machius et al., *Crystal structure of calcium-depleted Bacillus licheniformis α-amylase at 2.2Å resolution*, 246 J. MOL. BIOL. 545 (1995).

57. According to Bott, the term 'Calcium binding site' "means a region within α-amylase which is suitable for and acts to bind a calcium ion in the presence of free calcium." (BX 2003 at col. 6, ll. 38-41.)

associated with

58. Bott does not appear to provide a specific definition for the term "associated with."

59. Bott does describe the location of the calcium binding site said to have been discovered by applicants: "The CalB binding site disclosed herein is located in the region where the A domain and the C domain interface." (BX 2003 at col. 8, ll. 32-34.)

Accordingly, we understand that Bott uses the term "associated with" to indicate that the calcium binding site "associated with" the A and C domains is physically "between" the A and C domains.

60. More particularly, Bott teaches that:

> [t]he segments of the α-amylase polypeptide chain which comprise the CalB binding site include residues 290-309, 339-347, 402-411, 426-436, and 472-477. These polypeptide segments comprise the CalB binding site. Accordingly, regiospecific random mutations in these regions would be expected to yield variants that modulate the stability of α-amylase via modulation of the affinity of calcium at this site.

(BX 2003 at col. 9, ll. 41-45.)

ligand residues

61. According to Bott, the terms '[l]igand residues' or 'calcium ligand' mean:

> an amino acid residue or residues within an α-amylase enzyme which forms a ligand with calcium ion bound within a calcium binding site. With respect to the calcium binding site within α-amylase discovered by Applicants, five amino acid ligands have been identified which are believed to act as calcium ligands. The calcium ligand residues comprise amino acid residues equivalent to G300, Y302, H406, D407, and D430 in *Bacillus licheniformis* α-amylase. Specifically with respect to these identified calcium ligands, the carbonyl oxygens of G300, Y302 and H406 and the side-chains of D407 and D430 are believed to be implicated in binding calcium.

(BX 2003 at col. 6, ll. 55-67.)

modified

62. Bott writes that "[a] 'modified' α-amylase is an α-amylase which has been subjected to genetic or chemical modification so as to change its biochemical, structural or physico-chemical properties." (BX 2003 at col. 5, ll. 54-57.)

to alter the characteristics of said calcium binding site

63. Bott writes that "[a]lteration of the calcium binding site may include reducing or increasing the affinity of the site to bind calcium ion." (BX 2003 at col. 6, ll. 48-50.)

64. Bott indicates that modifications to increase the stability of the enzyme preferably "are within 15 angstroms of th center of mass of the calcium bound to the CalB binding site,

more preferably within 10 angstroms of the cent4r of mass of the calcium bound to the CalB binding site." (BX 2003 at col. 8, ll. 43-46.)

thereby alter the performance of said alpha amylase

65. According to Bott, "[b]y altering the performance is intended to mean the stability (e.g., oxidative or thermal) or the activity (e.g., the rate or efficiency with which the α-amylase hydrolyzes starchy substrate) of the enzyme in its various applications." (BX 2003 at col. 6, ll. 50-54.)

by substituting an amino acid residue at a position corresponding to one or more of, Q298 . . .

66. According to Bott, "[a] residue of a precursor α-amylase is equivalent to a residue of *Bacillus licheniformis* α-amylase if it is either homologous (i.e., corresponds in position for either the primary or tertiary structure) or analogous to a specific residue or portion of that residue in *Bacillus licheniformis* α-amylase (i.e., having the same or similar functional capacity to combine, react, or interact chemically or structurally.)" (BX 2003 at col. 8, ll. 57-63.)

67. Bott teaches that homology to the primary structure is established by comparing the amino acid sequence of a precursor "to the *Bacillus licheniformis* α-amylase primary sequence and particularly to a set of residues known to be invariant to all

α-amylases for which sequences are known . . . It is possible also to determine equivalent residues by tertiary structure analysis of the crystal structures reported for [certain amylases]." (BX 2003 at col. 8, l. 66, through col. 9, l. 4; figure cite and subsequent literature cites omitted.)

Scope of the Bott invention

68. Bott teaches that "[t]he α-amylases according to the present invention comprise an amino acid sequence which is derived from the amino acid sequence of a precursor α-amylase." (BX 2003 at col. 7, ll. 47-49.)

69. Bott also teaches that its invention is not limited to mutations of the particular mature α-amylase of *B. licheniformis*, but it extends to precursor α-amylases that contain "amino acid residues at positions which are equivalent to the particular identified residue in *Bacillus licheniformis* α-amylase." (BX 2003 at col. 8, ll. 52-57.)

Svendsen disclosure relating to terms in Svendsen claim 113 and the Count

α-amylase

70. According to Svendsen's 563 specification, "α-Amylases (α-1,4 glucan-4-glucanohydrolase, EC 3.2.1.1) constitute a group of enzymes which is capable of hydrolyzing starch and other

linear and branched 1,4-glucosidic oligo- and polysaccharides." (SX 1007 at 1, ll. 11-13.)

71. The "industrially important *Bacillus* α-amylases," which Svendsen calls "Termamyl-like α-amylases," are central to Svendsen's disclosure. (SX 1007 at 2.)

72. According to Svendsen, the term "'Termamyl-like α-amylase' is intended to indicate an α-amylase which, on the amino acid level, exhibits a substantial homology to Termamyl®,[8] i.e. the *B. licheniformis* α-amylase SEQ ID NO:2" (SX 1007 at 5, ll. 7-9; SEQ ID NO:2 at 74-75; hereafter abbreviated as "BLA".)

73. Two especially closely related α-amylases are the *B. amyloliquefaciens* α-amylase (SEQ ID NO:4; "BAA") and the *B. stearothermophilus* α-amylase (SEQ ID NO:6; "BSA"). (SX 1007 at 4.)

74. Svendsen identifies several other α-amylases that it regards as Termamyl-like α-amylases. (SX 1007, at 4, l. 19, through 5, l. 6.)

75. More specifically, according to Svendsen, substantial [amino acid sequence] homology requires "at least 60% . . . homology with at least one of" Svendsen's disclosed SEQ ID NO: 2, 4, or 6, or SEQ ID NO: 1 or 2 of WO 95/26397 [BX 2013] or in

---

[8] Following Svendsen, we shall not repeat the marking of this term as a registered trademark in expressions such as "Termamyl-like."

Tsukamoto et al., 1988 [not of record]." (SX 1007 at 5, ll. 10-14.)

76. Svendsen states that amino-acid sequence homology may be determined by use of conventional algorithms. (SX 1007 at 5, ll. 19-23.)

77. Svendsen provides further definitions of homology based on immunological cross-reactivity and DNA hybridization with Termamyl-like α-amylases. (SX 1007 at 5, ll. 14-18.)

A and C domains

78. Svendsen describes the overall structure of α-amylase as follows:

> the α-amylase structure is made up of three globular domains ordered A, B, and C, with respect to sequence, which lie approximately along a line in the order B, A, C. The domains can be defined as being residues 1-103 and 206-395 for domain A, residues 104-205 for domain B, and residues 396-483 for domain C, the numbers referring to the *B. licheniformis* α-amylase (SEQ ID NO:2).

(SX 1007 at 8, ll. 3-7, underscored text added per amendment F_2.)[9]

79. According to Svendsen, "[d]omain A is the largest domain and contains the active site." (SX 1007 at 8, l. 12.)

---

[9] See application file 09/327,563, Paper 11 at 2. The text of the exhibit is crossed by a vertical line and is accompanied by a marginal note, "sub F_1," which indicates, in the former practice of the USPTO with paper files, that the paragraph has been amended in a paper labeled "F," which in this case is Paper 11. (Paper 11, pages 1 through 3 are attached as an appendix to this decision.)

80. Domain A is said to be defined as residues 1-103 and 206-395 in BLA. (SX 1007 at 8, l. 5.)

81. Svendsen states further that loop 3, also called "domain B," is an extended loop between strand 3 and helix 3 of domain A. (SX 1007 at 9, ll. 1-8.)

82. Domain B is said to be defined by residues 104-205 in BLA. (SX 1007 at 8, l. 5-6.)

83. Svendsen also writes, "Domain C is the C-terminal part of the protein consisting of amino acids 396-483. Domain C is composed entirely of β-strands which forms [sic] a single 8-stranded sheet structure, which folds back on itself, and thus may be described as a β-sandwich structure. . . . One part of the β-sheet forms the interface to domain A." (SX 1007 at 9, ll. 27-31.)

<u>calcium binding site</u>

84. Svendsen describes the calcium binding site between the A-C domain as follows:

> One calcium ion is located between the A and C domain . . . which is also the one best coordinated (IUM 503) includes a carbonyl backbone from Gly300 [G300], Tyr302 [Y302] and His406 [H406], atom OD2/OD1 from Asp430 [D430], atom OD1 from Asp407 [D407], and one water molecule"

(SX 1007 at 10, ll. 18-21).

associated with

85. Svendsen does not appear to recite the phrase "wherein said calcium binding site is associated with said A domain and said C domain."

86. On the basis of its description of the calcium binding site, quoted *supra*, we understand that "associated" means "between."

ligand residues

87. Svendsen does not appear to use the term "ligand residue" in its specification, but Svendsen refers to "coordinating residues," which appear to be the same thing. (SX 1007 at 10, ll. 8-17, listing the residues involved in the A/B calcium binding site between the A and B domains).

modified

88. Svendsen provides a definition of "modified" as follows:

> the term 'modified' as used in step ii) in the method according to the first aspect of the invention is intended to have the following meaning: When used in relation to an amino acid residue the term is intended to mean replacement of the amino acid residue in question with another amino acid residue.

(SX 1007 at 13, ll. 13-16.)

to alter the characteristics of said calcium binding site

89. Svendsen describes a "first aspect" of its invention as comprising analyzing the structure of a Termamyl-like α-amylase for amino acid residue(s) or structure(s) that are expected to affect some property of the enzyme, and modifying the protein accordingly to alter that property. (SX 1007 at 3, ll. 1-13.)

90. Svendsen discusses an aspect of its invention as decreasing the Ca^{2+}-dependency of Termamyl-like α-amylases. (SX 1007 at 23-27.)

91. More specifically, Svendsen states that "[t]he decreased Ca^{2+} dependency of the variant of the invention may advantageously be achieved by increasing the Ca^{2+} binding affinity of the parent Termamyl-like α-amylase, in other words the stronger the Ca^{2+} binding of the enzyme, the lower is the Ca^{2+} dependency." (SX 1007 at 23, ll. 27-30.)

92. Svendsen states that "[i]t is presently believed that amino acid residues located within 10Å from a sodium or calcium, ion are involved in or are of importance for the Ca^{2+} binding capability of the enzyme." (SX 1007 at 24, ll. 1-3.)

93. Svendsen states further that residues may be substituted to improve calcium binding on the basis of several factors, including stabilizing contacts between the A, B, and C domains, or the domains as such. (SX 1007 at 25, ll. 1-19.)

thereby alter the performance of said alpha amylase

94. Svendsen provides a broad description of its invention as follows:

> [t]he property which may be altered by the above methods of the present invention may, e.g., be substrate specificity, substrate binding, substrate cleavage pattern, temperature stability, pH dependent activity, pH dependent stability (especially increased stability at low (e.g. pH<6, in particular pH<5) or high (e.g. pH>9) pH values), stability towards oxidation, Ca^{2+}-dependency, specific activity, and other properties of interest.

(SX 1007 at 4, ll. 6-10.)

by substituting an amino acid residue at a position corresponding to one or more of, Q298 . . .

95. Svendsen discusses the identification of corresponding amino acid residues in an α-amylase that differs from the model as follows, "[t]he corresponding part in other homologous α-amylases may easily be identified on the basis of a comparison of the amino acid sequences and/or three-dimensional structures of the respective α-amylases." (SX 1007 at 17, ll. 5-7.)

96. Svendsen also writes: "For instance, the basic principle of structure comparison is that the three-dimensional structures to be compared are superimposed on the basis of an alignment of secondary structure elements (such as the central 8 β-strands in the barrel) and the parts differing between the structures can subsequently easily be identified from the

superimposed structure." (SX 1007 at 12, ll. 19-23.)

97. According to Svendsen, the structure of Svendsen's model does not come from a naturally occurring α-amylase:

> [t]he Termamyl-like α-amylase (SEQ ID NO:13) which was used to elucidate the three-dimensional structure forming the basis for the present invention consists of the 300 N-terminal amino acids of the *B. amyloliquefaciens* α-amylase (with the amino acid sequence shown in SEQ ID NO:4) and amino acids 301-483 of the C-terminal end of the *B. licheniformis* α-amylase with the amino acid sequence SEQ ID NO:2. The bacterial α-amylase belongs to the "Termamyl-like α-amylase family" and the present structure is believed to be representative for the structure of any Termamyl-like α-amylase.

(SX 1007 at 7, ll. 19-25.)

98. Regarding residues that affect ion binding, Svendsen writes:

> It is presently believed that amino acid residues located within 10Å from a sodium or calcium ion are involved in or are of importance for the Ca^{2+} binding capability of the enzyme.
>
> Accordingly, the variant according to this aspect of the invention is preferably one, which has been modified in one or more amino acid residues present within 10Å from a calcium and/or sodium ion identified in the three-dimensional Termamyl-like α-amylase structure in such a manner that the affinity of the α-amylase for calcium is increased.
>
> The amino acid residues found within a distance of 10Å from the Ca^{2+} binding sites of the *B. licheniformis* α-amylase with the amino acid sequence SEQ ID NO:2 . . . are as follows:
> <list of ~110 residues>

(SX 1007 at 24, ll. 1-18.)

99. The ~110 member list of "10 Å" residues includes all the residues listed as being coordinating residues of the calcium ion bound between the A and C domains. (SX 1007 at 10, ll. 18-21.)

100. All the amino acid residues recited in Svendsen claim 113, but for residues F403 and L427, are included in the ~110 member list of residues.

101. Regarding residue 403, in a section headed "Random Mutagenesis" (SX 1007 at 39, l. 8), Svendsen teaches further:

> For region-specific random mutagenesis with a view to improving the thermal stability of a parent Termamyl-like α-amylase, codon positions corresponding to the following amino acid residues of the *B. licheniformis* α-amylase (SEQ ID NO:2) may appropriately be targeted:
>
> <u>To improve the stability of the calcium site between Domain A and C</u>
> I428-A435
> T297-L308
> F403-V409
>
> * * *

(SX 1007 at 39, ll. 12-20; indentation modified for clarity.)

102. The only reference to residue 427 in Svendsen's involved application appears to be at page 32, in a section titled, "Variants with increased thermostability and/or altered temperature optimum." Svendsen writes:

> In order to fill a hole in the vicinity of the active site mutation to any other amino acid residue of an amino acid residue corresponding to one or more of the

following residues of the *B. licheniformis* α-amylase (SEQ ID NO:2) is contemplated:

L427, V481

Of interest is a mutation to a more bulky amino acid residue.

Of particular interest is a variant of a Termamyl-like α-amylase which comprises a mutation corresponding to one or more of the following mutations in the *B. licheniformis* α-amylase (SEQ ID NO:2):

L427 F, L, W
V481, F, I, L, W

(SX 1007 at 32, ll. 22-31, underscored text added per amendment "F_3".)[10]

103. In the same thermostability section, Svendsen suggests substitution at the F343 position:

In order to fill a hole in the vicinity of the active site mutation to any other amino acid residue of an amino acid residue corresponding to one or more of the following residues of the *B. licheniformis* α-amylase (SEQ ID NO:2) is contemplated:

F350, F343

Of interest is a mutation to a more bulky amino acid residue.

Of particular interest is a variant of a Termamyl-like α-amylase which comprises a mutation corresponding to one or more of the following mutations in the *B. licheniformis* α-amylase (SEQ ID NO:2):

F350W
F343W

(SX 1007 at 32, ll. 12-21, underscored text added per amendment F_3.)[11]

---

[10] *See* application 09/327,563, Paper 11 at 3 (copy appended to this decision). The label "F 3" is a clerical error, as the previous amendment was labeled F_3.

[11] *See* application 09/327,563, Paper 11 at 2-3 (copy appended to this decision).

Scope of Svendsen's invention

104. According to Svendsen, its invention is quite general:

> Generality of structure
>
> Because of the high homology between the various Termamyl-like α-amylases, the solved structure defined by the coordinates of Appendix 1 is believed to be representative for the structure of all Termamyl-like α-amylases. A model structure of other Termamyl-like α-amylases may easily be built on the basis of the coordinates given in Appendix 1 adapted to the α-amylase in question by use of an alignment between the respective amino acid sequences. The creation of a model structure is exemplified in Example 1.
>
> The above identified structurally characteristic parts of the Termamyl-like α-amylase (Ca-binding site, substrate binding site, loops, etc.) may easily be identified in other Termamyl-like α-amylases on the basis of a model (or solved) structure of the relevant Termamyl-like α-amylase or simply on the basis of an alignment between the amino acid sequence of the Termamyl-like α-amylase in question with that of the *B. licheniformis* α-amylase used herein for identifying the amino acid residues of the respective structural elements.

(SX 1007 at 11, ll. 10-23.)

105. Regarding extensions of its invention, Svendsen states:

> It will be understood that amino acid residues or fragments found in corresponding positions in other α-amylases, in particular fungamyl-like α-amylases, may be used as a template for the construction of the variant according to the invention. The corresponding part in other homologous α-amylases may easily be identified on the basis of a comparison of the amino acid sequences and/or three-dimensional structures of the respective α-amylases.

(SX 1007 at 17, ll. 5-7.)

III. The motions

Construction of Bott's claims

i. Svendsen preliminary motion 4

106. Svendsen moves for judgment that Bott claims 1-28 are indefinite under 35 U.S.C. § 112, second paragraph. (Paper 31.)

107. According to Svendsen, one skilled in the art would read all of Bott's claims as requiring:

> modified α-amylases comprising an A domain, a C domain, and a calcium binding site, wherein:
> - said calcium binding site is associated with said A domain, and
> - said C domain comprises ligand residues in said A domain and/or said C domain.

(Paper 31 at 4, fact 5; and at 13-15.)

108. Svendsen urges that Bott's claims are therefore indefinite because "it makes no sense to one skilled in the art" to say that the C domain can comprise ligand residues in the A domain. (Paper 31 at 14.)

discussion

The predecessor to the Federal Circuit instructed that "[c]laims are definite if they set out and circumscribe a particular area with a reasonable degree of precision and particularity." *In re Moore*, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971). Moreover, "[w]e must read the claims, not in a vacuum, but in light of the prior art and the disclosure, as one

of ordinary skill in the art." *Id.* "Only after a thorough attempt to understand the meaning of a claim has failed to resolve material ambiguities can one conclude that the claim is invalid for indefiniteness. Foremost among the tools of claim construction is of course the claim language itself, but other portions of the intrinsic evidence are clearly relevant, including the patent specification and prosecution history." *All Dental Prodx, LLC v. Advantage Dental Products, Inc.*, 309 F.3d 774, 780, 64 USPQ2d 1945, 1949 (Fed. Cir. 2002).

Bott claim 1, parsed according to Svendsen's construction, reads as follows:

> An α-amylase comprising an A domain, a C domain and a calcium binding site,
>
> wherein
> [1] said calcium binding site is associated with said A domain
> and
> [2] said C domain comprises ligand residues in said A domain and/or said C domain,
>
> wherein
> said α-amylase is modified to alter the characteristics of said calcium binding site and thereby alter the performance of said α-amylase by substituting an amino acid residue at a position corresponding to one or more of . . . .

(square bracketed numbers added). In this reading, clause [1] modifies the previously recited term "calcium binding site,"

while clause [2] modifies the previously recited term "C domain."

A second reading is:

An α-amylase comprising an A domain, a C domain and a calcium binding site,

wherein said calcium binding site
[1'] is associated with said A domain and said C domain
[2'] comprises ligand residues in said A domain and/or said C domain

wherein
said α-amylase is modified to alter the characteristics of said calcium binding site and thereby alter the performance of said α-amylase by substituting an amino acid residue at a position corresponding to one or more of
. . .

In this second reading, the phrases [1'] and [2'] both modify the previously recited term "calcium binding site." Within phrase [1'], the phrases "said A domain" and "said C domain," are parallel, and explain that the calcium binding site is "associated with" both domains. Phrase [2'] adds the further limitation that the calcium binding site comprises "ligand residues," that is, residues that are chemically bonded to the calcium ion, in either or both of the A or C domains.

As Svendsen notes, and as Bott concurs, phrase [2] in Svendsen's reading of Bott's claims, "said C domain comprises ligand residues in said A domain and/or said C domain," is "nonsensical," and does not correspond to what Bott disclosed in

its specification as its invention. On the other hand, the second reading makes sense internally and comports with what Bott describes in its specification as being its invention. We further note that both parties both agree that the language of the Bott claims is improved grammatically by the addition of the conjunction "and" between phrase [1'] and phrase [2']. (*See* Svendsen claims 77 et seq., which were amended (Paper 11, "Mark-up amendment," at 4) in response to a requirement by the examiner (Paper 10 at 4; *see also* Bott preliminary motions 7 and 8 (Papers 38 and 39, respectively).) Moreover, Svendsen has not directed our attention to any evidence in the record that Bott ever relied on the reading espoused by Svendsen. Nor has Svendsen shown that either Bott or the examiner ever understood the claims to mean something different from what was disclosed in the specification. On the record before us, it is apparent that the omission of the word 'and' from Bott's claims was "inadvertent and unnoticed." *Cf. I.T.S. Rubber Co. v. Essex Rubber Co.*, 272 U.S. 429, 441 (1926).

We hold that the claims as written are susceptible to only the second reading, *supra*. Our reading of Bott's claims is not, "in any real sense, a remaking of the claim, but is merely giving to it the meaning which was intended by the applicant and understood by the examiner." *Essex*, 272 U.S. at 442 (1926).

Neither party argues that the latter reading is indefinite. Accordingly, Svendsen preliminary motion 4 is DENIED.

ii. Bott preliminary motion 8 and Svendsen preliminary motion 12

109. Bott preliminary motion 8 seeks: (1) to substitute "[Bott] Count 2," in which the word –and– is inserted between the phrase "and said C domain" and the phrase "comprises ligand residues in said A domain and/or said C domain"; and (2), to delete one of the two commas between "D407" and "G410".

Our construction of Bott claim 1, which defines an alternative of Count 2, reads identically to proposed Bott Count 2. Accordingly, Bott preliminary motion 8 is DISMISSED as moot.

Svendsen preliminary motion 12, for benefit of earlier filed applications with regard to Bott Count 2, is contingent on the grant of Bott preliminary motion 8. That contingency has not been met, so Svendsen preliminary motion 12 is DISMISSED as moot.

Count 2

Bott preliminary motion 5

110. Bott argues in preliminary motion 5 that there is no interfering subject matter[12] between any of Bott claims 1-28 and

[12] We use this term, defined in Bd.R. 203(a), in place of the now obsolete term "interference-in-fact," which was used by Bott and defined in former Board Rule 601(j).

any of Svendsen claims 192-206 and 208-213 under the "two-way" test endorsed by the Federal Circuit under the pre-September 2004 rules (*Eli Lilly v. Board of Regents of the Univ. Wash.*, 334 F.3d 1264, 1269, 67 USPQ2d 1161, 1164 (Fed. Cir. 2003), *cert. denied*, 124 S.Ct. 1713, 158 L.Ed.2d 416 (2004) and adopted expressly under the post-September 2004 rules (37 CFR § 41.203(a)). (Paper 40 at 9-10.)

111. Bott preliminary motion 5 is contingent on a decision that Svendsen claims 77-81, 84-88, 90-92, 97, 113-118, and 120, are not patentable to Svendsen. (Paper 40 at 1.)

112. As will be seen, this contingency is met in our decision on Bott preliminary motion 3, *infra*.

113. In the redeclaration of this interference, claim 192 was set as an alternative definition of Count 2. (Paper 121 at 12.)

In order to insure that we decide issues relevant to the determination of priority, we take up Bott preliminary motion 5 at this point to resolve the proper relation of Svendsen claims 192, 194-196, 198-201, 203, 204, 206, and 208 to Bott's involved claims.

114. Svendsen claim 192 reads as follows:

> A variant of a parent α-amylase, said parent alpha-amylase having SEQ ID NO. 2, in which variant the amino acid residues 325-345 of the parent α-amylase have been

> replaced with amino acid residues 294-313 of SEQ ID No. 10.

115. The residues to be replaced, 325-345, include residues Q340 and F343 of SEQ ID NO:2.

116. SEQ ID NO:10 specifies a particular α-amylase of interest, which is made by the fungus *Aspergillus oryzae*, and is commercially available as FUNGAMYL®. (SX 1007 at 15, ll. 22-25; and at 17, ll. 1-2.)

117. Svendsen teaches that Termamyl-like α-amylases may be modified to take on characteristics of "non-Termamyl-like α-amylases" by substituting "loops," i.e., chains of amino acid residues from one α-amylase to another. (SX 1007 at 3, ll. 14-25 and at 8, ll. 30-32.)

118. In one specific variant of the invention, the amino acid residues 325-345 of SEQ ID NO:2, which constitute loop 8 of BLA, are replaced by the amino acid fragment corresponding to amino acid residues 294-313 of SEQ ID NO:10. (SX 1007 at 23, ll. 12-15.) This specific variant is the subject matter of Svendsen claim 192.

119. Svendsen describes the structure of α-amylases, including the "loops," as follows:

> Domain A of all known α-amylase structures have the same overall fold, viz. the (beta/alpha)8 barrel with 8 central beta strands (number 1-8) and 8 flanking α-helicies. . . . The C-terminal end of Beta strand 1

> is connected to helix 1 by a loop denoted loop 1 and an identical pattern is found for the other loops. These loops show some variation in size and some can be quite extensive.
>
> The 8 central Beta-strands in the (beta/alpha)8 barrel superimpose well between the various known α-amylase structures, and this part of the structure, including the close surrounding of the active site located at the c-terminal end of the beta-strands, show high similarity between the different amylases.
>
> The loops connecting beta-strands and alpha helicies display high variations between alpha amylases. The loops constitute the structural context of the active site and the majority of the contacts to the substrate is found among residues located in these loops. Such important characteristics as substrate specificity, substrate binding, pH/activity profile, starch cleavage pattern are determined by the amino acids and the positions of same in these loops.

(SX 1007 at 8, ll. 15-29.)

120. Svendsen also teaches that:

> When two or more parts of the structure of the parent Termamyl-like α-amylase are modified so as to resemble the corresponding parts of the non-Termamyl-like α-amylase it is possible to increase the resemblance to the non-Termamyl-like α-amylase of the Termamyl-like α-amylase variant and thus to alter the properties of said variant in the direction of those of said non-Termamyl-like α-amylase. Loop modifications are discussed in much further detail further below.

(SX 1007 at 14, ll. 12-17.)

121. Svendsen claim 193 reads as follows (strikethrough and emphasis added):

> A variant of a parent alpha-amylase, said **variant** having an amino acid sequence which differs from the amino acid sequence of said parent, **wherein the**

> **difference** between said variant and said parent **consists of** a different amino acid residue in said variant than in said parent **at one or more positions selected from the group consisting of** the **positions which correspond** to amino acid residues Q298, G299, G301, ~~Y302~~, L307, F343, F403, H405, ~~H406~~, D407, L427, ~~I428~~, D430, and G475 in Bacillus licheniformis alpha-amylase (SEQ ID NO:2); wherein said variant has alpha-amylase activity.

The stricken text corresponds to species claimed in claims 197, 202, and 205 that have been deemed unpatentable to Svendsen (Paper 121 at 11).

122. The Svendsen claims that depend from claim 183 and that remain patentable to Svendsen are 194-196, 198-201, 203, 204, 206, and 208.

123. These claims name a single amino acid residue that is to be replaced from the list of residues recited in claim 193.

124. Claim 200 is representative:

> The variant according to claim 193, wherein said difference between said variant and said parent consists of a different amino acid residue in said variant than in said parent at the position which corresponds to amino acid residue F403 in *Bacillus licheniformis* alpha-amylase.

125. The combined limitations of claims 193 and 200 read:

> A variant of a parent alpha-amylase, said variant having an amino acid sequence which differs from the amino acid sequence of said parent, wherein said difference between said variant and said parent consists of a different amino acid residue in said variant than in said parent at the position which corresponds to amino acid residue F403 in *Bacillus licheniformis* alpha-amylase (SEQ ID NO:2); wherein said

variant has alpha-amylase activity.

126. Svendsen teaches that residue F403 may be targeted for substitution "[t]o improve the stability of the calcium site between Domain A and C." (SX 1007 at 39, ll. 14-20.)

127. Bott claim 1 reads:

> An α-amylase comprising an A domain, a C domain and a calcium binding site, wherein said calcium binding site is associated with said A domain and said C domain comprises ligand residues in said A domain and/or said C domain, wherein said α-amylase is modified to alter the characteristics of said calcium binding site and thereby alter the performance of said α-amylase by substituting an amino acid residue at a position corresponding to one or more of, Q298, G299, G301, Y302, L307, N309, Q340, F343, F403, H405, H406, D407,, G410, L427, I428, D430, G433, K436, N473, G474 and G475 in *Bacillus licheniformis*.

128. Bott claim 1 requires that the α-amylase be modified at at least one residue corresponding to one of the recited residues.

129. Residues Q340 and F343 are recited in Bott claim 1 and also in Bott claims 14 and 15, respectively, as residues that may be substituted in order to meet the limitations of the claims.

130. Residue F403 is recited in Bott claim 16, which reads:

> An α-amylase comprising an A domain, a C domain and a calcium binding site, wherein said calcium binding site is associated with said A domain and said C domain comprises ligand residues in said A domain and/or said C domain, wherein said α-amylase is modified to alter the characteristics of said calcium binding site and thereby alter the performance of said α-amylase by substituting an amino acid residue at a position

corresponding to F403 in *Bacillus licheniformis*.

131. Bott's specification also discloses that substitution of F403 is of particular interest:

> a cavity at the interface between domain A and domain C in the CalB region [A/C binding site] is bordered by [list of six residues]. Substitutions to reduce the size of the cavity, increase hydrophobicity and improve the complementarity of the A domain-C domain interface may improve stability of the enzyme. Specifically, modification of the specific residue at these positions with a difference residue selected from . . . may improve performance. Additional substitutions which may be useful are at V409 and F403, preferably the substitutions . . . at F403 comprise tyrosine or tryptophan.

(BX 2003 at col. 10, ll. 31-43.)

the arguments

132. In Bott's own words, "[w]hile Bott Claims 1-28" are sufficient to render obvious Svendsen Claims 192-206 and 208-213, the reverse is not true." (Paper 40 at 10.)

Svendsen claim 192

133. As for claim 192, Bott urges that it "is simply totally distinct from the claims of Bott, and neither set renders the other obvious." (Paper 40 at 10.)

134. More specifically, Bott argues that "Svendsen Claim 192 is directed to a single species, a chimer [sic:chimera]. It is not clear whether, due to modifications made to loop 8, this chimer even retains the A domain, C domain, and A/C calcium

binding site required by the Bott claims." (Paper 40 at 12.)

135. Bott argues further:

> The subject matter of Claim 192 is not required to exhibit α-amylase activity, and it is not clear from the '563 application whether in fact such activity is exhibited by this chimer. Certainly, Claim 192 of Svendsen does not require alteration of the A/C calcium biding site, if present, and does not require alteration of the performance characteristics of an α-amylase. It is, again unclear as to what characteristic this polypeptide may have, based on Claim 192 and the '563 application. As far as the reader is aware, it may not even constitute an α-amylase."

(Paper 40 at 12.)

136. Finally, Bott urges that the only characteristic that the subject matter of Svendsen claim 192 and the subject matter of Bott's claims share is that they are the product of manipulation. In Bott's words, "[t]his, alone, is not enough to suggest obviousness." (Paper 40 at 12.)

137. Bott has not directed our attention to any testimony regarding the effects of substitution of entire loops in α-amylases.

Svendsen claims 193+

138. Bott urges that Svendsen claims 193 and higher do not recite four limitations that Bott regards as critical to its claimed invention (Paper 40 at 10-11):

a. the Svendsen claims do not require that the

α-amylase have an A domain, a C domain, and an A/C calcium binding site;

b. the Svendsen claims do not require that the variants be non-natural;

c. the Svendsen claims do not require that the A/C calcium binding site be altered;

d. the Svendsen claims do not require that that alteration result in an alteration of the performance characteristics of the α-amylase.

139. Bott argues further that neither the prior art, nor Svendsen's 563 application, teaches that the variants encompassed by the Svendsen claims "would in fact exhibit the properties specifically recited by the Bott claims." (Paper 40 at 11.)

140. According to Bott, the state of the art was such that, as of Svendsen's filing date, properties of variants covered by Svendsen's claims were unpredictable. (Paper 40 at 11, citing the Declerck declaration, BX 2037, ¶ 22 and ¶¶ 26-29.)

141. In these paragraphs, Declerck testified that the direction of the effect of substituting one amino acid residue for another in a protein was not predictable, citing studies that she and coworkers had done (e.g., *Joyet 1992* (BX 2022); *Declerck 1990* (BX 2018); *Holm* (BX 2006), discussed *infra*). (BX 2037, ¶ 22 and ¶¶ 26-29.)

142. Bott does not direct our attention to the limitations of any particular claim.

discussion

Bott has chosen to argue exclusively that the subject matter of Svendsen's claims does not anticipate or render obvious the subject matter of Bott's claims. (Paper 40 at 10 and 12). As the moving party, Bott has the burden of proof. Bd.R. 121(b).

Svendsen claim 192

With regard to Svendsen claim 192, Bott's arguments are devoid of citation to evidence of record. Bott urges that "[i]t is not clear whether, due to modifications made to loop 8, this chimer even retains the A domain, C domain and A/C calcium binding site required by the Bott claims." (Paper 40 at 12.) Bott also urges that "[t]he subject matter of Svendsen claim 192 is not required to exhibit α-amylase activity, and it is not clear from the '563 application whether in fact such activity is exhibited by this chimer. . . . it may not even constitute an α-amylase." (Paper 40 at 12.) The point of this argument appears to be that the subject matter of Svendsen claim 192, taken as prior art, does not anticipate the subject matter of any Bott claim.

Bott does not deny that the polypeptide recited in Svendsen claim 192 is not within the compositional limits of Bott's

claims. In particular, Bott does not dispute that residues Q340 and F343 of BLA (SEQ ID NO:2) are changed when the loop substitution is made. Rather, Bott's arguments are solely that the A and C domains, the A/C binding site, and the altered characteristics are not met. Bott, however, has not addressed the claim in the context of the teachings of Svendsen's specification, which indicate that central beta-strand/alpha-helix barrel "show[s] high similarity between the different amylases," while the loops are highly variable from one α-amylase to another and are responsible for the substrate specificity and other characteristics of the amylase activity. (SX 1007 at 8, ll. 20-29.) Moreover, Bott has not directed our attention to any testimony or art of record that substantiates its attorney "argument." Accordingly, having failed to establish a factual basis for any of the conclusions Bott would have the Board draw, Bott's motion fails to prove that Svendsen claim 193 does not anticipate Bott claims 1 , 14, or 15.

Bott next asserts that the only common characteristic of the subject matter of Svendsen claim 192 and the subject matter of any of Bott's claims is that they are all "the product of manipulation." (Paper 40 at 12.) Bott's argument against the presumed obviousness of its claims over the subject matter of Svendsen claim 192 is, "[t]his [common characteristic of

artificiality], alone, is not enough to suggest obviousness." (Paper 40 at 12.)

Obviousness is a conclusion of law based on facts, including the content of the prior art, the level of ordinary skill in the art at the time the invention was made, the differences between the prior art and the claimed subject matter, and whether there would have been motivation, arising out of teachings in the prior art, the ordinary knowledge of one skilled in the art, or the nature of the problem. Bott has failed to direct our attention to any basis in the record for any of the "facts" it asserts or implies. As we do not accord significant weight to mere attorney argument, we conclude that Bott has not shown that the polypeptide of Svendsen claim 192 does not render obvious any Bott claim.

Svendsen claims 193+

Bott urges that, under the "two-way" test, there is no interfering subject matter between any of the Svendsen claims dependent on Svendsen claim 193 and any of Bott claims 1-28. In Bott's words, "[w]hile Bott Claims 1-28 are sufficient to render obvious Svendsen Claims 192-206 and 208-213 obvious, the reverse is not true." (Paper 40 at 10.) In other words, Bott relies solely on arguments that Svendsen's claims, taken as prior art, neither anticipate nor render obvious Bott's claims. Bott

focuses on the properties recited in Bott claims 1-28, and urges that "[n]othing in the '563 application, or in the prior art, informs those of skill in the art if any of the variants embraced by the Svendsen claims would in fact exhibit the properties specifically recited by the Bott claims." (Paper 40 at 11.) Thus, Bott appears to assert that Svendsen's claims, taken as prior art, do not anticipate any of Bott's claims. We note that Bott has not directed our attention to any particular claim of either party.

A difficulty with Bott's anticipation argument is that Svendsen claim 200, for example, clearly encompasses BLA, SEQ ID No:2, modified by substituting another amino acid residue for F403, i.e., phenylalanine at residue number 403. Moreover, Svendsen's specification teaches that the thermal stability of a parent Termamyl-like α-amylase may be improved by substitution at F403, which may improve the stability of the calcium binding site between the A and C domains. (SX 1007 at 39, ll. 12-20.) If the thermal stability of the parent α-amylase is "improved," α-amylase activity must be retained in the modified α-amylase. Similarly, if the stability of the calcium binding site between the A and the C domains is "improved," that bonding site exists in the modified α-amylase. Thus, Svendsen teaches BLAs modified by substitution at residue F403, as recited in Svendsen

claim 200, that "alter the characteristics of said calcium binding site [i.e., the one "associated with said A domain and said C domain"] and thereby alter the performance of said α-amylase," as recited in Bott's claims. Such modified α-amylases are clearly within the compositional scope of Bott claims 1 and 16. Under these circumstances, the subject matter of Svendson claim 200, if prior art, would anticipate Bott claims 1 and 16. Similar arguments hold for the remainder of Svendsen claims 194-196, 198-201, 203, 204, 206, and 208.

More generally, Bott teaches, in its specification, that

> [t]he segments of the α-amylase polypeptide chain which comprise the CalB binding site include residues 290-309, 339-347, 402-411, 426-436, and 473-477. These polypeptide segments comprise the CalB binding site. Accordingly, regiospecific random mutations in these regions would be expected to yield variants that modulate the stability of α-amylase via modulation of the affinity of calcium at this site. [BX 2003 at col. 9, ll. 41-45.]

It is apparent by inspection that all of the residues recited in Svendsen claims dependent on Svendsen claim 193 are in segments of the α-amylase chain that Bott identifies as comprising the CalB [A/C] binding site. Accordingly, to the extent that Bott's teaching can be practiced, a matter we shall consider under enablement, it would appear that all of the altered α-amylases within the scope of Svendsen's claims would be expected to have an altered A/C calcium binding site and altered α-amylase

characteristics. Similarly, whether Svendsen recognized and adequately taught that modified α-amylases within the scope of its claims would have the recited properties are matters relevant to the written description and enablement requirements, not to anticipation.

Finally, the alleged requirement that Bott's claimed compositions are "non-natural" is not a "limitation" that can serve to distinguish Bott's claims from Svendsen's. To the extent that either party's claims read on naturally occurring α-amylases, they are unpatentable because they are products of nature.

Bott's attempt to prove that its claimed subject matter is patentably distinct because its claims are not anticipated by Svendsen's claimed subject matter therefore fails.

Bott argues that Svendsen's claims do not render obvious Bott's claims because Svendsen's claims do not require or suggest the modified α-amylases having an A domain, a C domain, or an A/C binding site. (Paper 40 at 10.) We first note that Svendsen's claims are limited to modified α-amylases in which the difference "consists of" a single amino acid residue that corresponds to a specified residue in BLA (SEQ ID NO:2) has been changed. Thus, modified α-amylases of the invention must be structurally sufficiently similar to BLA that such corresponding amino acid

residues may be identified. The testimony of Declerck on which Bott relies (Paper 40 at 10, first full paragraph, citing BX 2037, ¶¶ 24-29, particularly ¶ 25) addresses the alleged relative lack of knowledge about the C domain and the uncertainty of the effects of substitutions. Declerck's testimony and Bott's arguments do not address whether α-amylases that are sufficiently similar to BLA (SEQ ID NO:2) that corresponding residues can be identified can be so different that they do not have A and C domains and an A/C calcium binding site. Accordingly, Bott's arguments that the structural limitations are not met or are not obvious are unsupported by evidence of record, and they must fail.

Bott urges that "[n]othing in the '563 specification [of Svendsen], or in the prior art, informs those of skill in the art if any of the variants embraced by the Svendsen claims would in fact exhibit the properties specifically recited by the Bott claims." (Paper 40 at 11.) Bott relies on the testimony of Declerck for the state of the art (BX 2037 at ¶¶ 22, 26-29) and the teachings of Svendsen's application (BX 2037 at ¶¶ 49-4). (Paper 40 at 11.) Bott appears to argue that, as a consequence, the requirement in its claims that the A/C calcium binding site be altered and that the performance of the modified α-amylase must thereby be modified would not have been obvious over

Svendsen's claims, which do not recite these properties.

Review of Svendsen's specification shows that Bott's and Declerck's characterizations of that document are overstated. First, Declerck points out that Svendsen identified the A/C calcium binding site in the α-amylase. (BX 2037 at 18, ¶ 50, citing SX 2001 at 10, ll. 18-24, where Svendsen identifies the amino acid residues that are coordinated to the calcium.) Thus, the position of the A/C calcium binding site is known. Bott also does not dispute that Svendsen identifies all residues within 10 Å of any calcium binding site. (*See* SX 1007 at 24.) Nor does Bott dispute that Svendsen provides coordinates based on an X-ray crystal structure of a chimeric α-amylase. (SX 1007, 45 pages following the figures.) Bott also does not dispute that many of the residues recited in the claims dependent on claim 193 are identified at page 24 of the Svendsen as being within 10 Å of a calcium binding site, including F403 (recited in claim 200), which we have discussed *supra*. Nor does Bott dispute that one skilled in the art, knowing where the A/C calcium binding site is, could readily determine which amino acid residues are within 10 Å of that site. Svendsen's specification indicates that substitutions of those "10 Å residues" would be considered to be involved in or be of importance to calcium binding and therefore enzyme activity. (SX 1007 at 24, ll. 1-3, and 19-32; cf. Bott's

specification, BX 2003 at col. 8, ll. 43-46.) Svendsen's specification also states residues may be substituted to improve calcium binding on the basis of stabilizing contacts between the A, B, and C domains, or the domains as such. (SX 1007 at 25, ll. 1-19.)

As for the "properties specifically recited by the Bott claims" (Paper 40 at 11), review of those claims indicates that those properties are "the characteristics of said calcium binding site" and "the performance of said α-amylase." Given the breadth of these terms, we have no difficulty finding that Svendsen's broad indications of the effects of substitution of amino acid residues within 10 Å of the calcium binding sites, together with the identification of the A/C calcium binding site, the atomic coordinates of the residues, are sufficient to inform those skilled in the art that the specified properties would be exhibited by the modified α-amylases.

It has not escaped our attention that Declerck disparages the sufficiency of the chimeric α-amylase as a representative structure for all α-amylases. (BX 2037 at 17, ¶ 46.) Declerck's criticisms appear to be based on Svendsen's failure to disclose the properties, particularly the thermal and catalytic properties, of the chimeric polypeptide it used for the structural analysis. (BX 2037 at 16-17, ¶ 45.) However,

Declerck also testified, "one could have used the 1995 BLA structure [*Machius 1995*] structure to model an engineer mutations in a Termamyl-like α-amylase . . . for this purpose, the '563 application provides no additional information." (BX 2037 at 17, ¶ 48 (emphasis added).) Here, Declerck does not indicate that Svendsen's structure was inadequate or wrong for such studies. We also note that Declerck mentions other α-amylase crystal structures (e.g., BX 2037, ¶ 44, citing *Machius 1995* (Ex 2005) and *Berger 1995*[13] (BX 2031); and ¶ 48, citing *Machius 1998*[14] (BX 2023)), but she does not compare the structure provided by Svendsen with the other structures and indicate in what ways, if any, the Svendsen structure is inaccurate or deficient.

In our view, neither Bott nor Declerck accurately identified the differences between the claimed subject matter, particularly with regard to the altered BLA (SEQ ID NO:2) α-amylases that are clearly within the scope of Svendsen's claims, and the broad functional properties recited in Bott's claims. As a consequence, their analysis of whether such differences would

---

[13] Gary D. Brayer et al., *The structure of human pancreatic α-amylase at 1.8 Å resolution and comparisions with related enzymes*, 4 *Protein Science* 1730 (1995).

[14] Mischa Machius et al., *Activation of Bacillus licheniformis α-amylase through a disorder → order transition of the substrate-binding site mediated by as calciu7m-sodium-calcium metal triad*, 6 *Structure* 281 (1998).

have rendered Bott's claimed subject matter, as a whole, to be nonobvious to those of ordinary sill in the art is not convincing.

We conclude that Bott has not carried its burden to show that the subject matter of Svendsen claims dependent on claim 193 does not render obvious the subject mater of Bott's claims that define alternatives of the Count.

Because Bott has failed to demonstrate that the Svendsen's claims neither anticipate nor render obvious Bott's claims, Bott preliminary motion 5 is DENIED.

Bott preliminary motion 6

Bott, in preliminary motion 6, seeks to designate Svendsen claim 192 as not corresponding to Count 1, based on the "two-way" test for correspondence required under *Eli Lilly*, 334 F.3d at 1271, 67 USPQ2d at 1166. (Paper 39 at 1.) The current count, Count 2 includes claim 192 as one of the count alternatives. Thus, claim 192 can be said to correspond exactly to the count. In view of our determination that Bott failed to show that Svendsen claim 192 is not a proper part of the Count, Bott preliminary motion 6 is DENIED.

Enablement

Bott preliminary motion 3

143. Bott urges that all of Svendsen's involved claims, namely, claims 77-81, 84-88, 90-92, 97, 113-118, 120, 192-206, and 208-213, lack an enabling disclosure. In Bott's view, undue experimentation, as gauged by application of the Wands factors, would be required to practice their full scope. (Paper 42 at 1 and 21-24.)

144. As a result of the redeclaration of this interference according to Count 2 (Paper 121 at 12-13), Bott preliminary motion 3 applies only to claims 77-81, 84-88, 90-92, 97, 113-118, 120, 192, 194-196, 198-201, 203, 204, 206, and 208.

145. Bott directs its arguments for lack of enablement of Svendsen's claims other than claim 192 to two major issues, one primarily structural, the second primarily functional.

146. The structural issue is, has Svendsen adequately taught how to determine what amino acid residues in what other α-amylases correspond to the recited amino acid residues of BLA (SEQ ID NO:2)?

If Svensen has not provided sufficient teachings, Bott argues that it would have required undue experimentation to determine which α-amylases to select for modification, and further undue experimentation to figure out which residues

"correspond" and are thus suitable for substitution. In other words, undue experimentation would have been required to make claimed α-amylases.

147. The functional issue is, has Svendsen adequately taught how to determine whether the A/C calcium binding site has been altered, and whether that alteration has altered the α-amylase performance?

Here, if Svendsen has not provided adequate teachings, Bott argues that it would have required undue experimentation to determine whether the substitution of the corresponding amino acid residues in fact resulted in alteration of the characteristics of the A/C calcium binding site, and whether those changes were responsible for any altered amylase (starch degrading) performance.

148. Initially[15], Bott argues that there is a "complete absence of knowledge of the relationship between primary structure (identity of the [sequence of] amino acid residues) and function, it is difficult to identify even potential candidates that satisfy the claims." (Paper 42 at 22.)

---

[15] Bott asserts that WO96/23874 (SX 1004), the published version of Svendsen's PCT priority document ("PCT"), is prior art to Svendsen, and that this affects Svendsen's enablement date. (Paper 42 at 1.) Bott does not appear to develop this argument elsewhere in its Brief. In particular, Bott does not offer an explanation of why the PCT is prior art even though the parent of Svendsen's involved application, which was filed as a continuation, prior to the publication of the PCT. Bott's arguments in this regard are frivolous, and waste the resources of the Board and the opposing party.

149. Declerck testified on behalf of Bott that the determination of which amino acids correspond to an equivalent position in a different α-amylase can be extremely difficult, particularly when there are insertions, substitution, and deletions in one sequence relative to another. (BX 2037 at 29, ¶¶ 83-84.)

150. Declerck asserts that some α-amylases do not contain corresponding amino acid residues, citing, as an example, α-amylase from *B. subtilis*, which it is said does not contain a residue that corresponds to Q298, G301, or Y302. (BX 2037 at 30, ¶ 85, citing *MacGregor*[16], BX 2032 at 405, fig. 1, top row).

151. Moreover, according to Declerck, even in "the highly homologous BAA and BStA," correspondences assigned on the basis of linear sequence alignments have been shown to be incorrect based on structural studies. (BX 2037 at 29, ¶ 83, citing *Suzuki 1989*[17] (BX 2028) and *Declerck 1990*[18] (BX 2018).)

152. According to Declerck, "[p]resent thinking is that only α-amylases from Bacillus organisms contain the A/C calcium

---

[16] E. Ann MacGregor, *α-Amylase structure and activity*, 7 J. PROTEIN CHEM. 399 (1987).

[17] Yutaka Suzuki et al., *Amino acid residues stabilizing a bacillus α-amylase against irreversible thermoinactivation*, 264 J. BIOL. CHEM. 18,933 (1989).

[18] Nathalie Declerck et al., *Use of amber suppressors to investigate the thermostability of Bacilus lichiformis α-amylase*, 265 J. BIOL. CHEM. 15481 (1990).

binding site, but even if claims 77-81, 84-88, 90-92, 97, 113-118, and 120 are restricted to variants of α-amylase from Bacillus species, this embraces an almost unlimited number of α-amylases given the teaching in the '563 application that the variants may contain additional insertions, substitutions, and deletions, and/or be comprised of hybrid sequences." (BX 2037 at 28, ¶80.)

153. Bott argues further that screening procedures and biochemical assays had not been developed and are not taught by Svendsen, to assess the impact of changes of residues on the properties of the α-amylases. (Paper 42 at 23.)

154. Declerck avers that "[s]etting up an experiment and screening method to identify a particular enzyme property is not trivial and it is not something one of skill would have been able to do without inventive effort." (BX 2037 at 32, ¶ 93.)

155. Declerck testified, on the basis of her personal experience in conduction research on amylase mutants, that the selection and characterization of mutants regarding a particular enzyme property was a limiting step in such research: "finding appropriate conditions for in vitro assays (including, e.g., temperature and time of incubation, pH, starch concentration, calcium concentration) allowing to detect variants with the desired altered property proved to be a daunting task." (SX 2037

at 11, ¶¶ 31-32.)

156. Declerck also stated that, "[o]nce possible targets [i.e., residues that are non-optimal for calcium binding] have been selected for analysis, choosing the most appropriate residues to be introduced to reach the desirable effect [i.e., to increase calcium binding] is again a difficult and highly speculative task, even when the crystal structure of the parent amylase is available." (BX 2037 at 22, ¶ 64.)

157. Declerck also states that "[c]omputer-aided molecular modeling is helpful in trying [to] identify potential residues to modify, however, even the model will have a varying range of predictability and high sequence homology helps but it is still not enough to identify with any certainty what substitutions will not destroy enzyme activity while providing for some other altered property." (BX 2037 at 33, ¶ 96.)

158. Bott also argues that even if amino acid residues in a potential candidate can be identified, the consequences of substitution would not have been foreseeable due to the lack of knowledge about the relation between structure and function in the α-amylase enzymes. (Paper 42 at 22.)

159. Declerck testified that in February 1996, there was no suggestion in the prior art about what substitutions would be of interest near the A/C interface, and that Svendsen's 563

application "offers no help whatsoever" in this regard. (BX 2037 at 32, ¶ 90.)

160. Svendsen urges that Bott "dramatically understates" value of the teachings provided by Svendsen's involved 563 application, particularly the complete 3-D structure of a representative Termamyl-like α-amylase. (Paper 71 at 14-15.)

161. Svendsen urges further that "[t]he crystal coordinates, in conjunction with prior knowledge of *in vitro* mutagenesis of α-amylases and the literature on α-amylases, enable one of skill in the art to accurately predict which amino residue substitutions will have an effect on various properties of the α-amylase." (Paper 71 at 17.)

162. Svendsen does not appear to cite any published experiments or authority in support of its allegation that reliable and accurate predictions of properties of modified α-amylases would have been within the ordinary skill of the art at the time its invention was made.

163. Moreover, Svendsen urges that its claims 77-81, 84-88, 90-92, 97, 113-118, and 120 are limited to Termamyl-like α-amylases, while its amended claims (added in Svendsen preliminary motion 10; presumably also the five claims permitted in Svendsen preliminary motion 13) are narrowly drawn to non-naturally occurring variants of three particular Termamyl-like

α-amylases, namely BLA, BAA, and BStA. (Paper 71 at 15.)

164. With regard to claim 192, which Bott characterizes as being directed to a single species, i.e., a unique chemical compound, Bott urges that Svendsen's application "totally fails to advance a utility" for the claimed sequence. (Paper 42 at 25.)

165. Bott urges further that Svendsen's specification "does not hint of what value the combination of the substitutions and deletions has, or how the mutant would be used." (Paper 42 at 25.)

166. Bott concludes that, in the absence of a disclosed utility or properties of the claimed polypeptide, the enablement requirement has not been met. (Paper 42 at 25.)

Principal witnesses

167. Dr. Nathalie Declerck ("Declerck") testified on behalf of Bott. Declerck represents that she has a Ph.D. in molecular and cellular genetics from the Institut National Agronomique Paris-Grignon. (BX 2037, Declerck declaration, at 1; BX 2016, Declerck curriculum vitae.) Declerck has numerous research publications relating to protein structure and function, including investigations of genetic modifications of the Bacillus lichiniformis α-amylase protein. (BX 2037 at 1; BX 2016 at 2-3.)

168. Dr. Torben V. Borchert ("Borchert") testified on behalf

of Svendsen. Borchert represents that he has a Ph.D. from the Technical University of Denmark. (SX 1022, Borchert curriculum vitae at 1.) Borchert has numerous research publications and is listed as an inventor on several patents relating to protein structure and function, including investigations of genetic modifications of the *Bacillus lichiniformis* α-amylase protein. (SX 1022 at 2-7.) Borchert is an inventor for Svendsen.

discussion

The enablement standard is met if the specification would have taught those skilled in the art, as of the filing date of the application for patent, enough such that, given what they already knew, they could have made and used the full scope of the claimed invention without "undue experimentation." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334, 65 USPQ2d 1385, 1400 (Fed. Cir. 2003). Whether experimentation would have been undue involves consideration of a number of factors, including "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Wands factors "are illustrative, not

mandatory. What is relevant depends on the facts." *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1136 (Fed. Cir. 1999), *citing Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991). Whether there is a reasonable correlation between the scope of the claims and the scope of enablement may depend critically on the degree of predictability of the relevant arts. *Plant Genetic Systems N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1340, 65 USPQ2d 1452, 1456 (Fed. Cir. 2003). The burden of proof is not lessened because the invention is in some way "pioneering." *Plant Genetic Systems*, 315 F.3d at 1339, 65 USPQ2d at 1455.

In the present case, the nature of the claimed invention is both subtle and complex. Embodiments of the invention include a modified protein in which a single specified amino acid residue out of more than 500 amino acid residues has been changed, with the aim of improving the binding of calcium at a particular site in the protein, and e.g., increasing the temperature range over which the protein will catalyze the degradation of starch. As will become apparent when we consider the breadth and content of the claims, the art as of the filing dates (early 1996) was nascent. Although the ability to change a particular residue at will appears to have been established, predicting and measuring

the resulting structure and changes in function were not routine. For example, the parties have not directed our attention to any examples of comparable modifications of enzymatic proteins, with concomitant prediction and control of properties. Nor have the parties directed our attention to any working examples in the Svendsen application within the scope of the count.

We do not doubt that the skill of the average worker in this area is and was extremely high. Such workers have advanced degrees in disciplines such as molecular biology, protein structure determination, molecular modeling, and kinetics. In the mid-1990's, such persons would have been familiar with techniques to manipulate and express genes encoding modified enzymes and with methods to begin to characterize enzyme properties. (Declerck, BX 2037 at 2, ¶2; Borchert, SX 1021 at 2, ¶3.) We also find that such persons would have been capable of solving complex problems requiring multi-disciplinary approaches. The question is whether they would have required "undue" experimentation to make and use the claimed subject matter.

We first consider the scope and content of Svendsen's claims. Claim 113, which is exemplary of the lower-numbered claims 77-81, 84-88, 97, 113-118, 120, reads:

> An alpha amylase comprising an A domain, a C domain and a calcium binding site, wherein said calcium binding site is associated with said A domain and said C domain

> and comprises ligand residues in said A domain and/or said C domain, wherein said alpha amylase is modified to alter the characteristics of said calcium binding site and thereby alter the performance of said alpha amylase by substituting an amino acid residue at a position corresponding to one or more of Q298, G299, G301, Y302, L307, F343, F403, H405, H406, D407, L427, I428, D430, and G475 in Bacillus licheniformis (SEQ ID NO:2).

Claim 200 is representative of the higher numbered claims 194-196, 198-201, 203, 204, 206, and 208, and reads as follows, incorporating the limitations of claim 193, from which it depends:

> A variant of a parent alpha-amylase, said variant having an amino acid sequence which differs from the amino acid sequence of said parent, wherein said difference between said variant and said parent consists of a different amino acid residue in said variant than in said parent at the position which corresponds to amino acid residue F403 in *Bacillus licheniformis* alpha-amylase (SEQ ID NO:2); wherein said variant has alpha-amylase activity.

Claims 113 and 200 share two structural requirements. First, α-amylases within the scope of the claims have A and C domains and a calcium binding site between the A and the C domains (A/C calcium binding site). The A/C calcium binding site must have "ligand residues," i.e., what Svendsen refers to as "coordinating residues" (SX 1007 at 10, ll. 8-17) in at least one of the A and C domains. All examples in the record have "ligand residues" in both the A and the C domains.

The second structural requirement is that α-amylases within

the scope of the claim must have at least one amino acid residue at a position "corresponding" to one of the recited amino acid residues of BLA. Generally, this means that the structure of the candidate polypeptide must be sufficiently similar to that of BLA that a particular amino acid residue may be said to provide a comparable structure and function as an amino acid residue in BLA (SEQ ID NO:2). Svendsen discusses the identification of corresponding amino acid residues in an α-amylase that differs from the model as follows, "[t]he corresponding part in other homologous α-amylases may easily be identified on the basis of a comparison of the amino acid sequences and/or three-dimensional structures of the respective α-amylases." (SX 1007 at 17, ll. 5-7.) Svendsen also writes: "For instance, the basic principle of structure comparison is that the three-dimensional structures to be compared are superimposed on the basis of an alignment of secondary structure elements (such as the central 8 β-strands in the barrel) and the parts differing between the structures can subsequently easily be identified from the superimposed structure." (SX 1007 at 12, ll. 19-23.) Thus, according to Svendsen, "corresponding residues" may be determined from the amino acid residue sequences of the protein or from a comparison of the three-dimensional structures of the protein (determined by x-ray diffraction analysis or estimated by

modeling based on the amino acid sequence, assuming that the protein is sufficiently similar to the model α-amylase provided by Svensen).

Claims 113 and 200 share the functional requirement, which is express in claim 200, but only implicit in claim 113, that the modified α-amylases are capable of hydrolyzing starch. (SX 2001 at 1, ll. 11-13.) No other useful property of this class of enzymes appears in the record. We therefore conclude that the claims and the term "α-amylase" are limited to active, i.e., starch-degrading, polypeptides.

Two other functional properties are recited in claim 113, but not in claim 200. The first of these is that substitution of another amino acid residue for one of the recited corresponding residues must "alter the characteristics" of the A/C calcium binding site. Regarding the alteration of the characteristics of the A/C calcium binding site of α-amylases, Svendsen writes:

> It is highly desirable to be able to decrease the Ca^{2+} dependency of a Termamyl-like α-amylase. Accordingly, in a further aspect the invention relates to a variant of apparent Termamyl-like α-amylase, which exhibits α-amylase activity and which has a decreased Ca^{2+} dependency as compared to the parent α-amylase . . . . **It is presently believed that amino acid residues located within 10Å from a sodium or calcium ion are involved in or are of importance for the Ca^{2+} binding capability of the enzyme.** Accordingly, the variant according to this aspect of the invention is preferably one, which has been modified in one or more amino acid residues present within 10Å from a calcium and/or

> sodium ion identified in the three-dimensional Termamyl-like α-amylase structure in such a manner that the affinity of the α-amylase for calcium is increased.

(SX 2001 at 23, l. 18, to 24, l. 7, paragraphing omitted, emphasis added.) Svendsen also notes several considerations that may be used as a basis for improving a calcium ion binding interaction of the enzyme: increasing the shielding provided by a residue by replacement with a bulkier residue (SX 1007 at 25, ll. 6-13); stabilizing contacts between the A, B, and C domains (*id.* at ll. 14-19); and protecting the calcium binding site or improving the coordination between the calcium ion and the residues that make up the binding site (*id.* at ll. 20-22).

The second recited functional requirement, again express only in claim 113, is that the altered characteristics of the A/C calcium binding site in turn "alter the performance" of the α-amylase. Regarding altered performance of the α-amylase, Svendsen writes:

> [t]he property which may be altered by the above methods of the present invention may, e.g., be substrate specificity, substrate binding, substrate cleavage pattern, temperature stability, pH dependent activity, pH dependent stability (especially increased stability at low (e.g. pH<6, in particular pH<5) or high (e.g. pH>9) pH values), stability towards oxidation, Ca^{2+}-dependency, specific activity, and other properties of interest.

(SX 1007 at 4, ll. 6-10.)

With the possible exception of an "accidental" degeneracy,

the change of the structure or composition of a molecule by changing the structure or composition of a part of the molecule results in a change in the properties of that molecule that can in principle, if not always in practice, be measured. Thus, the second and third functional requirements, which arise out of a change in structure or composition, are mere recitations of inherent properties of the claimed modified molecules.

Regarding these structural and functional requirements, only the determination of the starch-degrading activity of the enzyme appears undisputedly to be a matter of routine. The parties dispute the enablement of the other requirements, namely (1) the structural characterization of an α-amylase for the presence of A and C domains, and an A/C calcium binding site; (2) the presence and identity of "corresponding amino acid residues"; (3) determining whether substitution leads to a change in the characteristics of the A/C calcium binding site; and (4) determining whether that change alters the performance of the enzyme. Although we regard the recited functional properties as inherent in the structure of the modified molecules, we must consider whether Svendsen, and in turn Bott, has taught those of ordinary skill in the relevant arts how to measure the effect on calcium binding at the A/C calcium binding site, and the resulting effect on the performance of the amylase, as their

claims require. "[I]t is for the invention as claimed that enablement must exist." *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983); *In re Hiniker Co.*, 150 F.3d 1362, 1369, 47 USPQ2d 1523, 1529 (Fed. Cir. 1998) ("the name of the game is the claim").

structure and corresponding amino acid residues

Generally, Bott urges that Svendsen has not provided sufficient information to establish the identity, in a candidate α-amylase, of what amino acid residues correspond to the recited residues in BLA (SEQ ID NO:2). (Paper 42 at 22.) These arguments apply to all the claims except claim 192, i.e., to claims 77-81, 84-88, 90-92, 97, 113-118, 120, 194-196, 198-201, 203, 204, 206, and 208. All of these claims contain the requirement that at least one amino acid residue corresponding to certain identified residues in BLA, SEQ ID NO:2, must be replaced by another amino acid residue. Again, the point is that if it would have required undue experimentation to identify which residues correspond to the named residues of BLA (SEQ ID NO:2), it would have required undue experimentation to make the claimed invention. Svendsen responds that the atomic coordinates of the model α-amylase that it disclosed in its specification provide the critical information necessary for the skilled worker to identify the corresponding residues via sequence alignment and

molecular modeling. (Paper 71 at 16-17.)

According to Declerck, "[p]resent thinking is that only α-amylases from Bacillus organisms contain the A/C calcium binding site, but even if claims 77-81, 84-88, 90-92, 97, 113-118 and 120 are restricted to variants of α-amylase from Bacillus species, this embraces an almost unlimited number of α-amylases given the teaching in the '563 application that the variants may contain additional insertions, substitutions, and deletions, and/or be comprised of hybrid sequences." (BX 2037 at 28, ¶80.) Svendsen urges that its claims 77-81, 84-88, 90-92, 97, 113-118, and 120 are limited to Termamyl-like α-amylases. Consistently, Borchert testified that although "[a]ll α-amylases comprise A and C domains and at least one calcium binding site" (SX 1021 at 19, ¶67), "the vast majority of α-amylases would not have this structural feature" (SX 1021 at 20, ¶68, emphasis added.)

We conclude that the potential scope of these claims is vast, and that, even if a relatively small number of all α-amylases qualify for modification, the number of species resulting from modifications that are encompassed by the claims is enormous.

The record indicates that, as of the mid-1990s, the determination of atomic coordinates by x-ray crystallography of protein crystals, although difficult, was more or less routine,

provided high quality crystals were available. The rub was that obtaining protein crystals suitable for x-ray structure determinations was far from routine. Borchert, for example, stated:

> at the time of filing of the '385 Patent, crystallization of α-amylase in general would have required an unreasonable amount of experimentation for one of skill in the art given the unpredictability in the art of crystallizing α-amylases and the very limited previous successes in doing so with bacterial α-amylases, including those of *Bacillus*. Exhibit 1007, p. 1, ll. 17-21. In fact, Svendsen's Danish application No. DK 0128/95 (Exhibit 1001) describes the first successful effort to crystallize a bacteria α-amylase having the metal ions (calcium, sodium) coordinate, after many failed attempts in the art, such as Machius (1995) who was only able to crystallize a calcium-depleted α-amylase. Exhibit 2005.

(SX 1021 at 16, ¶51; emphasis added). According to Borchert, the situation had not changed as of September 2004: "to my knowledge no scientists have come up with the crystal structure of the native Bacillus licheniformis alpha-amylase despite the fact that many people have tried." (Borchert deposition, BX 2055 at 39, l. 19, to 40, l. 1.) In fact, Svendsen does not report in its specification the crystal structure of a native α-amylase. Svendsen only describes the structure of a chimeric protein – an artificial construct of α-amylases from two different Bacillus α-amylases. Declerck also testified that many groups had tried and failed to obtain crystals of BLA for x-ray analysis in the

period 1990-1996. (BX 2037 at 28, ¶79; BX 2053 at 184-194.)[19] Bott's involved 385 patent does not contain the atomic coordinates for the crystal structure it says it solved.

We find on this record that the art of protein crystallization is unpredictable. We find further that there are no teachings in Svendsen's application that generally advance the art of α-amylase crystallization. Thus, if it would be necessary to determine the crystal structure of any other α-amylase in order to determine whether it had resides corresponding to the BLA (SEQ ID NO:2) residues recited in the claims, the ordinary worker would have required undue experimentation to make the claimed invention. Accordingly, we next consider whether additional protein crystal structures would have been necessary to determine whether an α-amylase had an A/C calcium binding site, and whether it contained amino acid residues "corresponding" to any of the residues of BLA recited in Svendsen's claims. In this regard, Declerck testified that it would be necessary to determine further crystal structures to find A/C calcium binding sites:

---

[19] At oral argument, counsel for Bott argued that the structural characterization of α-amylases by x-ray analysis, determining whether an A-C binding site exists, and the sequencing and subsequent determination of corresponding amino acid residues were routine: "These events take time, but that doesn't make them extraordinary." (Paper 150 at 15-16.) This statement is at odds with the testimony of both Declerck and Borchert regarding the x-ray structural determination. Moreover, it is unsupported by objective evidence. We decline to give any weight to unsupported arguments of counsel.

> Certainly in 1996, no one working in this field would have known based on amino acid sequence alignments which of the universe of α-amylases contained this feature and a crystal structure would be necessary to identify whether the A/C calcium binding site was present. As evidence of the difficulty this presents, consider that between 1990 and 1996 numerous groups attempted to crystallize BLA in the presence of calcium and failed (Exhibit 2019, Declerck 1995, p. 1029, col. 2, 1st full ¶). It was also widely recognized that the bacterial α-amylases are the most diverse in terms of physio-chemical properties (Exhibit 2009, Nielsen, p. 254, col. 2, last ¶).

(BX 2037 at 28, ¶79.) Moreover, Declerck testified that crystal structures would probably be necessary to determine which residues actually correspond when comparing proteins when one has deletions of amino acid residues relative to the other:

> Q [counsel for Svendsen]: With that knowledge [of the crystal structure] and the knowledge of the sequence that you already had, would a person skilled in the art be able to identify a corresponding residue in any other Termamyl-like alpha amylase?
>
> A [Declerck]: Yes, except for deletions . . . it's only when you get really the structure of the two proteins that you can tell, oh, these are the two residues which are deleted.
>
> * * *
>
> it is normally simple to find a corresponding residue, but you don't need a structure for that.
>
> Q: You don't even need the structure for that.
>
> A: No. But for most residues, <u>exempt [sic] for maybe there are deletions, little deletions that appears in some Termamyl-like alpha-amylases, and for this you need the structure of both, until you can really be sure</u> that this is – these are the three residues that were deleted, I mean to be sure. <u>You can make a good guess, but maybe – normally only until you get the</u>

structure of both that you can tell.

(BX 2053 at 200, l. 5, through 201, l.9; emphasis added.)

Borchert also testified that a crystal structure would be necessary:

> Figure 5 of the Bott '385 Patent provides an alignment of primary structures of *B. licheniformis*, *B. amyloliquefaciens* and *B. stearothermophilus*, which are recited in Claim 3 of that patent. However, it is impossible to determine whether amino acid residues of α-amylases falling within the scope of Claims 1-2 and 4-28 of the Bott '385 Patent "correspond in position" at the level of the tertiary structure to an amino acid residue of the Bacillus licheniformis α-amylase without knowing the tertiary, i.e. crystal, structure of the *Bacillus licheniformis* α-amylase, including atomic coordinates. A comparison at the level of tertiary structure cannot be made using only an alignment of the linear amino acid sequences, other than with the highly homologous α-amylases recited in Claim 3 of the Bott '385 Patent, *i.e.*, *B. licheniformis*, *B. amyloliquefaciens*, and *B. stearothermophilus*.

(SX 1021 at 23, ¶ 77.)

The difference between the parties on this point is that Svendsen maintains that providing the atomic coordinates for the chimeric α-amylase in its specification was both necessary and sufficient for the enablement of the subject matter of its claims. In particular, Svendsen urges that "[t]he crystal coordinates, in conjunction with prior knowledge of *in vitro* mutagenesis of α-amylases and the literature on α-amylases, enable one of skill in the art to accurately predict which amino residue substitutions will have an effect on various properties

of the α-amylase." (Paper 71 at 17.) At oral argument, Svendsen urged that "[t]he difference between Svendsen and everyone else is that we provided a starting point for the three-dimensional structure of the enzyme upon which one of ordinary skill in the art could homology[20] build and determine what enzyme was inside or outside the scope of the claim." (Paper 150 at 36.)

The absence of crystal structures of other α-amylases for comparison with the structure provided by Svendsen, and the unrebutted testimony by Declerck that the physico-chemical properties of bacterial α-amylases were known to be "the most diverse," weigh against Svendsen's position that the crystal structure it provided is representative of all α-amylases. Moreover, Borchert's testimony that computer modeling would have sufficed to determine structures of other α-amylases given only their sequence is not supported by prior art publications indicating that comparable work had not been achieved with other enzymatic proteins. We credit Declerck's testimony that as of the mid-1990s filing dates of the parties, sufficiently reliable predictions of the structure of a related protein could not be made, particularly when one or more amino acid residues were

[20] We understand Svendsen to mean that one skilled in the art would start from the known structure it provided and derive the structure of the modified enzyme by treating the substituted amino acid residues as perturbations on the reference structure. This procedure assumes that the effects of substitution are relatively small and do not result in large changes of protein conformation.

"missing" relative to the model protein. Thus, we are led to the conclusion that additional crystal structures would have been required to assess properly what are the residues, if any, that "correspond" to the recited residues of BLA, SEQ ID NO:2.

Accordingly, we hold that Svendsen claims 77-81, 84-88, 90-92, 97, 113-118, 120, 194-196, 198-201, 203, 204, 206, and 208 lack an enabling disclosure based on the difficulty and the necessity of obtaining further x-ray crystal structures to identify the corresponding residues that are to be modified in candidate α-amylases, and thus, to make and use the claimed invention.

functional property: determination of binding site properties and enzyme performance

Bott argues that even after amino acid residues in a potential candidate have been identified, it would have required undue experimentation to determine whether the functional properties have been met. In other words, having modified an α-amylase at a specified corresponding residue, Bott maintains that it would have been too difficult to determine whether the invention had been made or used, i.e., whether the functional limitations had been fully met. Under such circumstances, undue experimentation would have required to make or use the claimed invention. Bott argues that the consequences of substitution of

different amino acid residues would not have been foreseeable due to the lack of knowledge about the relation between structure and function in the α-amylase enzymes. (Paper 42 at 22.) Declerck cited several examples, based on her own research and the research of others, as showing that the direction of effects, especially due to multiple substitutions in amylase mutants, was not predictable. (BX 2037 at 9-10, ¶¶ 24-26.) Moreover, Declerck testified that the studies had shown that the substitutions were "'protein specific', that is, they varied greatly in their effects from enzyme to enzyme, and a particular substitution in one α-amylase that might be beneficial in terms of improving properties, would, in a homologous enzyme or variant, be neutral or even detrimental." (SX 2037 at 10, ¶ 28.)

Bott argues further that screening procedures and biochemical assays had not been developed to assess the impact of changes of residues on the properties of the α-amylases. (Paper 42 at 23.) Moreover, Bott urges that Svendsen's 563 specification does not teach how to perform the assays and screening procedures necessary to determine whether the residue substitution has modified the A/C calcium binding site, and whether that modification has altered the performance of the enzyme. (Paper 42 at 23.) Declerck testified, on the basis of her personal experience in conduction research on amylase

mutants, that the selection and characterization of mutants regarding a particular enzyme property was a limiting step in such research. (BX 2037 at 11, ¶ 31.) In particular, Declerck stated that "finding appropriate conditions for in vitro assays (including, e.g., temperature and time of incubation, pH, starch concentration, calcium concentration) allowing to detect variants with the desired altered property proved to be a daunting task" (SX 2037 at 11, ¶ 32), and provided specific examples of experimental difficulties and complications (*id.* at 12). There was, according to Declerck, no screen or assay reported in the literature that could be generalized beyond the specific conditions of the test. (SX 2037 at 12, ¶ 33.)

At oral argument, counsel for Svendsen, citing the testimony of Borchert and Declerck, stated, "[i]t is our position that you cannot test to determine whether you alter a particular calcium binding site." (Paper 150 at 28.) The difference between Svendsen's disclosure and Bott's disclosure, according to Svendsen, is the crystal structure provided by Svendsen. (Paper 150 at 30, ll. 10-13.) Svendsen argues that Bott "dramatically understates" value of the teachings provided by Svendsen's involved 563 application, particularly the complete 3-D structure of a representative Termamyl-like α-amylase. (Paper 71 at 14-15.) Svendsen urges further that "[t]he crystal

coordinates, in conjunction with prior knowledge of *in vitro* mutagenesis of α-amylases and the literature on α-amylases, enable one of skill in the art to accurately predict which amino residue substitutions will have an effect on various properties of the α-amylase." (Paper 71 at 17.)

Borchert also testified:

> The atomic coordinates of the calcium-bound form of an α-amylase enable one skilled in the art to reasonably predict the contribution of an amino acid residue to the structural integrity of a calcium binding site, and thereby predict what amino acid substitutions will enhance, or detract from the structural integrity of the calcium binding site, for example to obtain higher affinity for calcium.

(SX 1021 at 17, ¶56.)

Svendsen and Borchert, however, cite scant published authority in support of their allegations that reliable and accurate predictions of properties of modified α-amylases would have been within the ordinary skill of the art at the time its invention was made. Svendsen quotes Declerck's review article, in which Declerck wrote, "Our BLA engineering project entered a new era when the X-ray crystal structure of the protein was solved." (Svendsen Opposition 3, Paper 71, quoting BX 2020[21], emphasis by Svendsen.) In Declerck's words, however, the new era "made it possible to investigate more rationally the stability

[21] Nathalie Declerck et al., *Engineering the thermostability of Bacillus licheniformis α-amylase*, 57/Suppl. 11 B IOLOGIA, BRATISLAVA 203, 207 (2002)

determinants by probing the role of possibly important protein regions and residues" (BX 2020 at 207, col. 1, last sentence; emphasis added.) We note there is a difference between 'more rational investigation' and 'reliable prediction' of properties of modified proteins. Svendsen also quotes a review article by Declerck (BX 2021[22]) published in 2003, in which the structure of the chimeric BAA-BLA polypeptide, reported in an article by Brozowski (SX 1037[23]), was said to have been used as part of the basis for modeling studies of a complex of an oligosaccharide with wild-type BLA and a hyperthermostable BLA variant. It is not clear from the remainder of this 2003 review article that the modeling was ever used to predict particular properties of a modified α-amylase, and that those predictions were later confirmed by experiment. Nor is the relevance of remarks in a paper submitted half a dozen years after the filing dates claimed for benefit of priority clear. Borchert also quotes a review article by Bott (SX 1016[24]), in which Bott wrote, "knowledge of

---

[22] Nathalie Declerck et al., *Hyperthermostabilization of Bacillus licheniformis α-amylase and modulation of its stability over a 50°C temperature range*, 16 PROTEIN ENG'G 287 (2003) (Marked as received 21 January 2002, revised 30 January 2003, and accepted 5 February 2003).

[23] Andrzej M. Brzozowski et al., *Structural analysis of a chimeric bacterial α-amylase. High-resolution analysis of native and ligand complexes*, 39 BIOCHEM. 9099 (2000). All of the Svendsen inventors are listed as co-authors.

[24] Richard Bott, *Analyzing three-dimensional structures of variant enzymes*, in ENZYME FUNCTIONALITY, DESIGN, ENGINEERING, AND SCREENING, 35, 38 (Allan Svendsen, Ed., 2003).

the three-dimensional structure of native and variant enzymes has been used to elucidate the underlying principles of stability, enzyme function, and energy conversion." (Borchert declaration, SX 1021 at 14-15, ¶46.) Neither Borchert nor Svendsen, however, have directed our attention to any discussion in the Bott reference (SX 1016) of the successful prediction of the properties of modified enzymes.

The record discloses a tension between those scientists who believe in the power of model-based predictions and those who accept them as indications that an experiment may be worthwhile. We find the following testimony particularly revealing:

> Q [by counsel for Svendsen]: Looking at your article at page 207 again, at the top of the next column it says "after careful inspection of the BLA structure, we chose 15 new targets." And I'm wondering how the knowledge of the structure enabled you to select the 15 targets.
>
> A: [by Declerck] That's – that's typical of our divergence between Machius [a coauthor] and I. . . . he really wanted to make it appear that we had designed the mutation. And I said, come on, Mischa, we cannot write that.
>
> Q: He believed that strongly in predicting the function from the structure, then?
>
> A: Well, I don't know what he believed really, but I mean, he wanted to make it appear we had designed the mutation after careful inspection. I mean, as I said to him, well, I have chosen the mutation sites. I just ask you to – I mean the eventual mutation site. And I just ask you to just look at the structure, since I couldn't do it myself, and tell me whether it's stupid

> or not, I mean in terms of if it's inside or it will disrupt substrate binding or be in the middle of a cavity, things I already suspected that was not the case, from what I knew.

(SX 2053 at 145, l. 12, through 146, l. 19.)

We declined to credit Svendsen's arguments regarding the efficacy of analysis of the single x-ray crystal structure provided in its specification to determine the existence and identity of corresponding amino acid residues. Similarly, we decline to credit Svendsen's arguments relating to the even more complex problem of determining the likely effect of substitutions on calcium binding or α-amylase properties. As the evidence indicates, and as Svendsen conceded (Paper 150 at 28), the experimental determination of whether the binding properties of the A/C calcium binding site have been altered, and whether there has been, as a consequence, an alteration in the performance of the modified α-amylase, would have required undue experimentation.

We conclude that determining whether the characteristics of a calcium binding site of a modified α-amylase have been altered, and whether that alteration in turn has altered the performance of the α-amylase, would have required undue experimentation by one skilled in the art as of the mid-1990s, notwithstanding the additional teaching of the chimeric α-amylase crystal structure

provided in Svendsen's application. Thus, undue experimentation would have been required to determine whether all the limitations of the claimed invention had been met, i.e., whether one had made (or used) an infringing invention. Accordingly, we hold that Svendsen claims 77-81, 84-88, 90-92, 97, 113-118, 120 lack an enabling disclosure.

In contrast, Bott's arguments with respect to claim 192 are without merit. As we found in our consideration of Bott preliminary motion 5, Svendsen teaches that modified α-amylases, in which the loop of an α-amylase has been replaced by the corresponding loop of a non-Termamyl α-amylase, take on some of the characteristics, e.g., the substrate specificity, pH/activity profile, etc., of the non-Termamyl α-amylase. (SX 1007 at 8, ll. 24-29 and at 14, ll. 12-17.) Declerck's testimony relating to the uncertainty of the effects of substituting residues does not address the replacement of loop 8 in BLA. Bott has not come forward with evidence sufficient to cast reasonable doubt on the teachings of the Svendsen specification regarding the subject matter of claim 192.

Bott preliminary motion 3 is GRANTED as to Svendsen claims 77-81, 84-88, 90-92, 97, 113-118, 120, 194-196, 198-201, 203, 204, 206, and 208; but DENIED as to Svendsen claim 192.

Svendsen preliminary motion 5

169. Svendsen moves for judgment that Bott claims 1, 2, and 4-28 lack an enabling disclosure. (Paper 32 at 2.)

170. According to Svendsen, the fundamental failure of Bott's specification is that it does not disclose the atomic coordinates of the complete crystal structure of a suitable reference α-amylase. (Paper 32 at 19.)

171. Svendsen urges that, as a consequence, Bott does not adequately teach[25]:

(a) how to determine which α-amylases may be modified for its invention, other than those recited in claim 3 (Paper 32 at 22);

(b) how to determine what amino acid residues in other α-amylases correspond to recited residues in BLA (Paper 32 at 23); and

(c) how to determine the characteristics of any specific calcium binding site within the α-amylase, and therefore the effect of modification on the performance of the α-amylase (Paper 32 at 23).

[25] We dismiss as frivolous Svendsen's arguments that Bott 's claims are not enabled based on its construction of Bott's claims as indefinite. By definition, the subject matter of an indefinite claim cannot be determined: but that circumstance is not a basis for a distinct statutory ground of unpatentability. Such arguments waste the resources of the opposing party and of the Board. The proper course was to file the present motion contingent on the denial of Svendsen preliminary motion 4.

172. Svendsen argues that, aside from Bott claim 3, which is limited to modifications of three specific α-amylases, Bott's specification provides no guidance as to what α-amylases should be modified to obtain the altered calcium binding and altered α-amylase performance. (Paper 32 at 22.)

173. Svendsen urges, with regard to item (a), that it is essential that the skilled artisan have a crystal structure of a representative α-amylase, in order to determine whether an α-amylase "otherwise falling within the scope of [Bott's claims] even has a calcium binding site associated with the A and C domains." (Paper 32 at 22.)

174. Regarding item (b), Svendsen argues that the state of the art was such that the atomic coordinates, obtained from a complete crystal structure of a suitable reference α-amylase, were (and are) required to guide the skilled worker to make "reasonable predictions" about which amino acids may be substituted "to arrive at a desired α-amylase property, e.g., higher affinity for calcium." (Paper 32 at 19-20, citing the Borchert declaration, SX 1021 [at 17], ¶ 56.)

175. More specifically, Svendsen urges that without providing atomic coordinates of the crystal structure, Bott does not teach how to determine what are amino acid residues at corresponding positions in an α-amylase other than highly

homologous proteins. Such determinations, according to Svendsen, require commensurate descriptions of the tertiary structures, which in turn requires at least one crystal structure. (Paper 32 at 23.)

176. Moreover, Svendsen argues that, "[a]t the time of the filing of the '385 Patent [Bott's involved patent] crystallization of α-amylases in general would have required undue experimentation, in light of the unpredictability in the art of crystallizing α-amylases and the very limited previous success in doing so." (Paper 32 at 21, citing BX 2005 (*Machius 1995*).)

177. Regarding item (c), Svendsen argues that assays to determine the calcium dependency of α-amylases "were not known to distinguish among individual calcium binding sites and the roles of each on overall calcium dependency." (Paper 32 at 21.)

178. Svendsen urges further that, although Bott's claims require that the modified α-amylase have modified characteristics of a specific calcium binding site, Bott's specification fails to teach how to determine the characteristics of any specific calcium binding site. (Paper 32 at 23.)

179. In this regard, Borchert testified:

> Those skilled in the art at the time of filing of the '385 Patent were familiar with assays for measuring the overall calcium dependency of α-amylases. However, in the case of α-amylases with more than one calcium binding site, such assays for measuring calcium

> dependency did not distinguish among the roles that the several calcium binding sites have on overall calcium dependency of the α-amylase. Thus, assays for measuring the overall calcium dependency of α-amylases could not have been used to measure alterations to characteristics of any one individual calcium binding site.

(SX 1021 at 14, ¶ 44.)

180. Svendsen urges that the Bott '385 patent does not include any working examples of an α-amylase within the scope of the claims. (Paper 32 at 24.)

181. Svendsen concludes that, guided only by Bott's specification, every modified α-amylase would have to be tested for altered calcium binding characteristics and consequent altered performance, and that this would require undue experimentation. (Paper 32 at 24.)

182. Bott responds that Borchert, one of the inventors for Svendsen, testified that Bott's 385 specification provided sufficient information to alter amino acids around the A/C calcium binding site and alter the properties of the enzyme. (Paper 82 at 15-16.)

183. Regarding the lack of an x-ray crystal structure, Bott urges that "[o]ne of skill in the art could easily repeat the very specific information provided in the example of the '385 patent for any amylase." (Paper 82 at 17.)

184. Moreover, according to Bott, the x-ray structures are

not essential for the practice of the invention, although they do help "prioritize" proposed modifications. (Paper 82 at 17, citing Borchert's testimony generally [presumably BX 2055, at 210, l. 21, to 211, l. 17, cited in Paper 82 at 12, item 46.]

185. As for the calcium binding assays, Bott urges that they are routine, relying on Borchert's testimony that the difference between the calcium dependency of the parent to the calcium dependency of the mutant would be attributable to a change in the calcium affinity at the A/C calcium binding site. (Paper 82 at 18.)

186. At oral argument, Bott urged that Bott's specification was not subject to Declerck's criticisms that the α-amylase performance assays were extremely limited in their scope of enablement, because Bott specifically defines the modification of the A/C calcium binding site and the performance of the α-amylase:

> the Bott patent in column 2 specifically and deliberately points to a collection of prior art, including Joyet and DeClerck, among others, that specifically describes certain reliable assays if you are only looking for affinity or stability. Remember that's how the Bott patent defines a modification of the AC binding site and an alteration of the performance of the enzyme.

(Paper 150 at 19, ll. 14-22.)

187. The Bott 385 patent, at col. 2, cites publications by

Declerck (BX 2018) and Joyet[26] (BX 2022), which are said to relate to stabilizing mutations in bacillus amylases. (BX 2003 at col. 2, ll. 29-31.)

188. The Bott 385 patent states, "[b]y altering the performance is intended to mean the stability (**e.g.**, oxidative or thermal) or the activity (**e.g.**, the rate or efficiency with which the α-amylase hydrolyzes starchy substrate) of the enzyme in its various applications." (BX 2003 at col. 6, ll. 50-54) (emphasis added).

189. According to the Bott patent:

> [b]ecause commercially available amylases are not acceptable under many conditions due to stability and/or activity problems, there is a need for an amylase having altered, and preferably increase, performance profiles under such conditions. For example, high alkalinity and oxidant (bleach) levels associated with detergents or the extreme conditions present during starch liquefaction can result in both destabilization and lack of activity from α-amylase. Thus, altered performance characteristics such as thermostability, pH stability, oxidative stability or calcium stability which can be achieved while also altering, maintaining, or increasing enzymatic activity as compared to the wild-type or precursor enzyme, would be desirable.

(BX 2003 at col. 3, ll. 37-49.)

190. Bott criticizes the remainder of Svendsen's application of the Wands factors as lacking evidence to support a conclusion

---

[26] Philippe Joyet et al., *Hyperthermostable variants of a highly thermostable alpha-amylase*, 10 BIOTECHNOLOGY 1579 (1992) (BX 2022).

of lack of enablement. (Paper 82 at 19.)

191. Bott claim 1 reads:

> An α-amylase comprising an A domain, a C domain and a calcium binding site, wherein said calcium binding site is associated with said A domain and said C domain comprises ligand residues in said A domain and/or said C domain, wherein said α-amylase is modified to alter the characteristics of said calcium binding site and thereby alter the performance of said α-amylase by substituting an amino acid residue at a position corresponding to one or more of, Q298, G299, G301, Y302, L307, N309, Q340, F343, F403, H405, H406, D407,, G410, L427, I428, D430, G433, K436, N473, G474 and G475 in *Bacillus licheniformis*.

discussion

As we have already determined, Bott claim 1 is substantially the same as Svendsen claim 113, the absence of the conjunction "and" between the phrases "said C domain" and "comprises ligand residues" being at most a typographical error. Not surprisingly, the definitions of the various terms of the claim are indeed easier to find in Bott's specification than in Svendsen's, and we find no substantial difference between the parties in the meaning of the terms or their relations to one another. We therefore need not embark on an extensive construction of Bott's claims. Suffice it to say that Bott's claims and Svendsen's claims are of comparably broad scope and potentially encompass an enormous number of species derived from a potentially enormous number of parent α-amylases.

As discussed at length in connection with Svendsen preliminary motion 5, the preponderance of the evidence of record indicates that the state of the art of α-amylase structure, as of Bott's filing date, was highly unpredictable, particularly in the absence of the crystal structure of a representative α-amylase. The weight of the evidence also indicates that obtaining crystals suitable for such analysis was highly unpredictable, time-consuming, and not a matter of routine, notwithstanding the high level of sophistication of the ordinary worker in this art. Thus, undue experimentation would have been required to determine whether an infringing embodiment had been made.

There is no dispute that Bott does not provide atomic coordinates based on the x-ray crystal structure described in Bott example 1 (BX 2003 at col. 13-14). We have already held that Svendsen's involved application, which does provide atomic coordinates, fails to provide sufficient structural data to enable one skilled in the art to determine, without undue experimentation, which α-amylases are sufficiently like BLA to be, potentially, within the full scope of the claims. Here, we find that Bott's specification does not provide sufficient additional information regarding the structure of α-amylases similar to BLA to guide those skilled in the art to select potential α-amylases. Furthermore, we find that the Bott

specification does not provide sufficient information to determine, for a given α-amylase that does contain A and C domains, and that binds calcium at a site between the A and C domains, which amino acid residues in the proposed α-amylase "correspond" to the recited BLA residues. The weight of the evidence indicates that, in many cases, a comparison of the crystal structures of BLA and a candidate α-amylase will be necessary to identify the corresponding residues. That effort, we have held, would have been undue; and Bott does not provide additional teachings that would have eased the labors of the ordinary worker to obtain relevant crystals for analysis. Accordingly, we hold that Bott provides insufficient guidance to determine, without undue experimentation, what are corresponding residues for the full scope of the claimed modified α-amylases, i.e., which residues should be substituted. Without knowing which residues to substitute, the claimed invention cannot be made. We note that our conclusion does not depend on an endorsement of Svendsen's argument that providing a BLA crystal structure suffices to enable such claims.

As for the functional recitations, Bott's argument that its specification specifically defines and limits the alteration of the performance of the α-amylase to altered affinity and stability, and that reliable assays for those properties were

disclosed, is belied by the specification itself. The definitions of the "altered characteristics" of the calcium binding site and of the "altered performance" of the α-amylase provided by Bott's specification are extremely broad. Oxidative and thermal stability are presented as examples of altered performance – other examples include stability under conditions of high alkalinity or oxidant (bleach) concentration, pH stability, and calcium stability. (BX 2003 at col. 3, ll. 37-49.) Bott's disclosure does not provide examples of assays for each of these properties, which, according to Declerck, require extensive experimentation to measure for each modified α-amylase. Thus, we reject Bott's arguments that its specification defines or limits the recited functional properties to those for which Bott teaches reliable assays.

Similarly, we find that Bott's teachings are insufficient to reduce to a routine level the experimentation required to determine whether a given substitution "alter[s] the characteristics of [the A-C] calcium binding site," and whether that substitution "thereby alter[s] the performance of said α-amylase." In addition to Borchert's direct testimony (SX 1021), we have considered his testimony on cross-examination (responding to Bott's lengthy questions with "That's correct," and "That is quite likely" (BX 2055 at 63, l. 13, and at 209, l. 17,

respectively). Although, we do not find Borchert's testimony particularly persuasive because he seldom provides the basis for his opinions by citation to publications or to experiments of which he has personal knowledge, his testimony in this regard is amply supported by the testimony of Declerck.

Declerck testified on the basis of her own research, work done by her immediate colleagues, and work published by others, that the development of assays and screening methods to determine if mutant α-amylases have altered properties, would have required "an enormous amount of work." (BX 2037 at 33, ¶ 94.) Among the factors contributing to the work, according to Declerck, is the necessity and difficulty of ensuring that the increased amylase activity is due to the increased activity of the enzyme rather than, e.g., more enzyme being present because expression has been increased by an inadvertent mutation of a gene regulatory sequence, or contamination by wild type enzyme. (BX 2037 at 32-33, ¶ 93.) Declerck testified that an additional difficulty is that, "[w]ith respect to screening methods . . . every parameter is significant, such as buffer composition, ionic strength, pH, temperature, and starch composition." (BX 2037 at 33, ¶ 95.) Under cross examination, Declerck testified that Joyet, in the work leading up to the *Joyet 1992* publication,

> was getting false positives because of increased

> production of – it was mutagenizing the old plasmid, the old gene. And so he got mutation that will increase the production of amylase, instead of having an amylase with increased thermostability, so – that you could be indeed misled in think you get a good mutant, in fact you've just got the gene with is better expressed, for instance. [BX 2053 at 83, ll. 3-11.]

Declerck also testified that, "[i]f you wanted to do the same thing for another amylase, then you have to go through the process again just to determine exactly what are the conditions if you want to see something." (BX 2053 at 92, ll. 13-16.) For example, Declerck explained that she had to develop a test to determine the relative thermal stability of mutants that are stable at 130°C under "ordinary" conditions. Because working at 130°C is not easy, her solution was to lower the calcium concentration until the mutants would be inactivated at a lower temperature. (BX 2053 at 96-97.) Declerck testified, "I don't think it was clear to me that, in fact, there was a clear relationship between stability and calcium affinity. I mean, there is an interdependency." (BX 2053 at 95, ll. 19-22.) She explained further, "well, now it seems obvious, but I'm not sure it was obvious to at that time, so that if I specifically wanted to screen for calcium dependency, then I will have a set of another experiments." Working to develop tests to assay for the influence of a particular parameter in a highly interdependent system in which many other parameters are significant, and in

which relationships among factors have not been established, does not, on this record, appear to be within the level of routine, ordinary skill.

Bott's disclosure lacks sufficient teachings to bring any of the factors within the level of ordinary skill of the art. We conclude that making and using the full scope of the invention claimed in Bott claims 1, 2, and 4-28 would have required undue experimentation. Svendsen preliminary motion 5 is therefore GRANTED.

Written Description

Bott preliminary motion 2

192. Bott moves for judgment that all of Svendsen's claims (except claim 192) lack an adequate written description. (Paper 43 at 1.)

193. Bott urges that Svendsen's 563 application lacks an adequate written description as of the 13 February 1996, filing date of the original parent, as well as of its 8 June 1999, filing date.[27] (Paper 43 at 1 and 19.)

194. Bott urges that Svendsen claims 77-81, 84-88, 90-92, 113-118, and 120 lack a description of a single species within

[27] We reject as frivolous Bott's argument that Svendsen's PCT document (SX 1004) is prior art against the Svendsen 563 application. See the discussion of Bott preliminary motion 3, *supra*.

the scope of those claims, and that there is no description of an altered A-C domain calcium binding site due to modification at any of the recited residues. (Paper 43 at 20-23.)

195. More particularly, Bott urges that Svendsen does not identify residues F403 (claims 85 and 113), L427 (claims 90 and 113), F343 (claims 84, 113, 193, and 199) and G427 (claim 204) as being correlated with the A/C calcium binding site. (Paper 43 at 22.)

196. Bott does not direct specific argument to the single residues recited for substitution in Svendsen claims 77-81, 86-88, 91, 92, or 97 (eleven claims).

197. Bott emphasizes that none of the these residues are identified as being within 10 Å of the A/C calcium binding site. (Paper 43 at 22-23.)

198. Bott urges further that although the claims recite the alteration of amylase properties generally, the only alteration taught is to decrease calcium dependency. (Paper 43 at 23.)

199. Bott urges that the claims dependent on claim 193 are directed to "α-amylase proteins that have a different primary structure when compared with their parents (amino acid sequence) but no differences in tertiary structure (folded or 3-D structure) and no differences in properties (the claims do not require 'altered' 'α-amylase activity.)" (Paper 43 at 24,

emphasis added.)

200. Bott urges further that the claims dependent on claim 193 are not restricted to 'Termamyl-like' α-amylases, whereas "whenever the Svendsen application addresses changing the A/C binding site, or decreasing calcium dependency, that discussion is expressly confined to such Termanyl-like α-amylases." Bott concludes that Svendsen never envisioned the modified non-Termamyl-like α-amylases with altered A/C binding site and altered calcium dependency embraced by these claims. (Paper 43 at 24.)

discussion

The written description requirement of 35 U.S.C. § 112, first paragraph, has been satisfied if the disclosure "reasonably conveys to a person skilled in the art that the inventor had possession of the claimed subject matter . . . ". *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1123, 72 USPQ2d 1785, 1790 (Fed. Cir. 2004), *quoting Eiselstein v. Frank*, 52 F.3d 1035, 1039, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995).

Of the fourteen residues named in claims that recite single residues for substitution, i.e., Svendsen claims 77-81, 84-88, 90-92, and 97, Bott specifically identifies only three, namely F403 (claim 85), L427 (claim 90), and F343 (claim 89), as lacking a written description. (Paper 43 at 22.) Bott urges that these

three residues are not identified by Svendsen's application as being correlated with the A/C binding site. Our own review of the Svendsen specification indicates that F403 is identified in the following passage:

> For region-specific random mutagenesis with a view to improving the thermal stability of a parent Termamyl-like α-amylase, codon positions corresponding to the following amino acid residues of the *B. licheniformis* α-amylase (SEQ ID NO:2) may appropriately be targeted:
>
> To improve the stability of the calcium site between Domain A and C
> I428-A435
> T297-L308
> **F403**-V409

(SX 1007 at 39, ll. 12-20; indentation modified for clarity; bold emphasis added.) On its face, this passage teaches that altering F403 will improve the stability of the A/C calcium binding site, yielding a modified α-amylase having improved thermal stability relative to the parent α-amylase. Thus, Bott's argument fails for at least residue F403.

Bott's focus on the alleged absence of "a single such substitution described anywhere in the '563 application" (Paper 43 at 21), and it's reliance on *In re Wallach*, 378 F.3d 1330, 71 USPQ2d 1939 (Fed. Cir. 2004) are misdirected. In *Wallach*, the issue was whether disclosure of a partial sequence of amino acids (ten out of 185-192) was sufficient to "describe" the DNA sequence for the entire protein. The Federal Circuit

held that "[w]hether Appellants were in possession of the protein says nothing about whether they were in possession of the protein's amino acid sequence." 378 F.3d at 1334, 71 USPQ2d at 1943. In that context, the court remarked, "such functional description can be sufficient only if there is also a structure function relationship known to those of ordinary skill in the art." *Id.* at 1335, 71 USPQ2d at 1943. In the present case, there is no dispute that Svendsen had possession of the complete amino acid sequence of the BL α-amylase, SEQ ID NO:2. Bott frames the issue as whether Svendsen adequately explained the relation between the structure of the modified α-amylases and their function – an issue that sounds in enablement. Bott, however, bears the burden of demonstrating that Svendsen's specification does not convey to those of ordinary skill in the art the subject matter now claimed, even if the disclosure is not express. That Bott's arguments fail to make this case is highlighted by Bott's failure to deal with each of the amino acid residues recited in each of the dependent claims that specify different individual residues that are to be substituted. Even as to residues F343, F403, and L427, Bott does no more than assert that they are not supported. Bott does not explain why the disclosure that is present for these claims is inadequate. We decline to act as an advocate for the moving party and

undertake, in the first instance, an analysis of the various factual issues underlying the adequacy of the disclosure in conveying possession of the claimed subject matter to those skilled in the art.

Accordingly, we find that Bott has failed to carry its burden with respect to Svendsen claims 77-79, 81, 84, 86, 90, 97, 113-118, and 120.

Bott also argues for lack of written description based on a proposed construction that the claims dependent on claim 193 are directed to modified proteins having no difference in tertiary structure from the parent protein. (Paper 43 at 24.) This argument is legally unsound. As a matter of law, the absence of limitations from a claim does not mean that embodiments having those limitations are excluded from the claimed subject matter. Such a proposition is at odds with the principle of peripheral claiming, that the fewer recited limitations, the broader the claim. If Bott's thesis is that the claims dependent on claim 193 are indefinite, that is no basis for the distinct thesis that they lack an adequate written description.

Bott next argues that the claims dependent on claim 193 are not restricted to "Termamyl-like" α-amylases, and are therefore not described because, in Bott's view, the Svendsen specification only discusses changing the A/C binding site of Termamyl-like

α-amylases. Again, Bott fails to explain why (assuming the premise for the sake of argument) that absence would have failed to convey to the ordinary workers in the art the various substitutions covered by those claims. Moreover, with the exception of claim 204 (reciting residue G427), which Svendsen concedes is not described (Paper 70 at 12, ¶ 76), Bott fails to address the specific residues recited in the claims dependent on claim 193, in connection with the limitations of those claims.

Bott preliminary motion 2 is GRANTED as to Svendsen claim 204, but is otherwise DENIED.

Svendsen preliminary motion 6

201. Svendsen seeks judgment that Bott's specification does not provide an adequate written description for Bott claims 1, 2, and 4-28. (Paper 33 at 2.)

202. Svendsen urges[28] that the written description requirement is not met because "atomic coordinates are the required 'blaze marks.'" (Paper 33 at 18.)

203. Svendsen urges further that without the atomic coordinates, it is impossible to determine what residues "correspond" to particular BLA residues. (Paper 33 at 21-24.)

[28] We dismiss as frivolous Svendsen's argument based on the alleged indefiniteness of Bott's claims. As noted *supra*, the proper procedure would have been to file the present motion contingent on the denial of Svendsen preliminary motion 4.

204. Svendsen also argues that Bott does not describe how to measure altered characteristics at the A/C binding site. (Paper 33 at 24-25.)

discussion

We shall not grant this motion, which sounds in enablement. The written description requirement is distinct from the enablement requirement. *See, e.g., Univ. Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 920 et seq. 69 USPQ2d 1886, 1890 et seq. (Fed. Cir. 2004) for an extensive discussion of the distinctions between the written description requirement and enablement. "The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to 'recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.'" *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003) (citation omitted). The detailed recitations in Bott's 385 patent leave no doubt that Bott described as its invention what it claimed: whether Bott successfully explained how to make and use the full scope of what it claimed is a separate inquiry.

Svendsen preliminary motion 6 is DENIED.

Svendsen's motion to suppress "evidence" from Bott's

specification as hearsay, is DISMISSED as moot with respect to Svendsen preliminary motion 5, which has been granted, and DISMISSED as moot with respect to Svendsen preliminary motion 6, because we have not considered that evidence in reaching those decisions.

Prior art motions

Bott preliminary motion 4

205. Bott moves for judgment that Svendsen claims 192-206 and 208-213 are "unpatentable as met (anticipate or obvious) by the prior art." (Paper 41 at 1.)

206. Nowhere does Bott explicitly state which of these claims are anticipated and which are obvious.

207. As the result of the decision of a merits panel of the Board that Svendsen is not entitled to a patent containing claims 193, 197, 202, 205, and 209–213 (Paper 121 at 13), Bott's motion is DISMISSED as to Svendsen claims 193, 197, 202, 205, and 209–213.

anticipation

208. Aside from Bott's identification of *Declerck 1990* (BX 2018) as teaching substitutions of H406 with eleven different amino acids, which meets the limitations of Svendsen claims 193, 202, and 209-213 (all of which have already been determined to be

unpatentable to Svendsen), Bott's sole argument for anticipation reads as follows:

> Nothing in the language of Claims 193-206 and 208-213 excludes natural products. All that is required is alignment with the BLA sequence to identify the specific position variation, and a hypothetical "parent" from which these can be derived. As only one example, the sequences for BLA and Aspergillus oryzae α-amylase (generally referred to as Taka-amylase) were available well prior to 1996. Exhibit 2037[29], ¶ 120. Simply aligning the two sequences shows a variation in the amino acid residues required. This can also be seen in Exhibit 2032[30], Figure 1. There the residue that corresponds to position Y302 differs in naturally occurring mutants (BstA is F at this residue) and the same is true for G475 of BLA). Exhibit 2006[31], page 185 at position 475 for sequences 2 and 3, respectively. Again, **selected** claims are anticipated thereby.

(Paper 41 at 9; emphasis added.)

209. *Holm 1991* (BX 2006), discloses the sequences of Taka-amylase (sequence 6), B. stearothermophilus amylase (BstA, sequence 7), and B. licheniformis (BLA, sequence 8), among others. (BX 2006 at 183-185, figure 1.)

discussion

Bott's statement of anticipation fails to identify which "selected" claims Bott considers to be anticipated by the

---

[29] Declerck declaration.

[30] E. Ann MacGregor, 7 J. PROTEIN CHEM. 399 (1988)

[31] Liisa Holm et al., *Random mutagenesis used to probe the structure and function of Bacillus stearothermophilus alpha-amylase*, 3 Protein Eng'g 181 (1990).

references. Bott, in its argument, fails to direct our attention to specific claims, and even fails to direct our attention to its claim charts. In any case, the claim charts are not argument: they are summaries of the evidence to assist the Board to determine whether references in fact teach (or suggest) the limitations as argued by the moving party. While one might speculate as to which claims Bott considers are anticipated, and which residues in the reference α-amylases Bott considers correspond to particular residues in BLA, SEQ ID NO:2, neither the opposing party nor the Board should be put in the position of synthesizing the movant's theory of its case. The burden of demonstrating a *prima facie* case of anticipation includes stating precisely which claims are anticipated, as well as explaining precisely what disclosure in the reference reveals all the limitations of the particular claims.

Bott's theory of anticipation also fails on the merits. The Svendsen claims dependent on claim 193 are drawn to compounds wherein the difference "consists of" substitution at the recited amino acid residue. However, comparison of the sequence of Taka-amylase (sequence 6) and BstA (sequence 7) that Bott cites as anticipating "selected claims" (perhaps Svendsen claim 80 (substitution at Y302) and Svendsen claim 97 (substitution at G475)) with the sequence of BLA (sequence 8), shows that there

are many differences in the sequences at positions other than those corresponding to Y302 or G475. (BX 2006 at 183-185, sequences 6-8.) Thus, none of these sequences can anticipate any of Svendsen's claims that are dependent on Svendsen claim 193.

Bott preliminary motion 4 is DENIED as to anticipation.

obviousness of claims 193+

210. Bott's argument for obviousness reads as follows:

> One of skill in the art would have expected, however, that any position could be the target for substitution, and based on the art identified, substitutions could be made that would give rise to some retained amylase property. Exhibit 2037, ¶ 123. The selection of one site over another does not constitute or require any particular creative skill, particularly because the entire sequence for BLA was known and the structure of the entire molecule had already been reported. . . . As the claims do not require any particular property, or utility, one of skill in the art would have expected, based on the art accumulated, that the claimed subject matter could have been prepared. More is not required for an unobviousness [sic: prima facie case of obviousness].

(Paper 41 at 10.)

211. The Declerck declaration, BX 2037, ¶ 123, essentially repeats the above-quoted argument without offering any further explanation.

Bott's statement of its case that claims that are not obvious are obvious suffers from the same defects as its case for anticipation. Bott fails to identify which claims which claims

are obvious over the prior art[32]. Moreover, Bott fails to identify the differences between the claimed subject matter and the prior art, which references provide the missing subject matter, and where the motivation to combine references or otherwise make up the differences is to be found. Bott's argument also fails to address the specific substitution of the claimed compounds, and fails to explain why those limitations, in combination as claimed, would have been obvious over specific teachings in the prior art. *In re Deuel*, 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

Again, Svendsen and the Board are left to speculate which claims Bott considers obvious, and what are the factual bases on which Bott would have us draw the legal conclusion of obviousness. Accordingly, this motion fails to show that Svendsen claims dependent on claim 193 are obvious over the prior art.

obviousness, claim 192

212. Bott argues that the polypeptide of claim 192 would have been obvious over the disclosures of either Suzuki (BX 2028)

[32] The mention of claims 209 and 210 (Paper 41 at 10) is irrelevant because they are no longer under consideration.

or Conrad[33] (BX 2029) of "exchanges" of [longer] amino acid sequences "that would include 325-345 of BLA." (Paper 41 at 11.)

Bott does not direct our attention to any disclosure in either reference that teaches or suggests the precise substitution recited in Svendsen claim 192. As a prima facie case of obviousness must be established with respect to every limitation of the claimed subject matter, this motion is DENIED as to Svendsen claim 192.

Bott preliminary motion 4 is DENIED.

Svendsen preliminary motion 7

213. Svendsen moves for judgment that Bott claims 1-7, 14, 18, 22, and 25 are unpatentable over prior art[34]. (Paper 34 at 1.)

Declerck 1990

214. Svendsen argues that Bott claims 1-3, 6, 7, and 18 are anticipated by Declerck 1990. (Paper 34 at 10.)

215. Bott claim 1 covers α-amylases in which one or more amino acid residues that correspond to certain specified amino

---

[33] Birgit Conrad et al., *Hybrid Bacillus amyloliquefaciens X Bacillus licheniformis α-amylases Construction, properties and sequence determinants*, 230 *Eur. J. Biochem.* 481 (1995).

[34] Again, Svendsen raises arguments based on its interpretation of Bott's claims as indefinite. For the reasons given previously, we dismiss these arguments as frivolous.

acid residues in BLA have been substituted, resulting in an alteration of the characteristics of the A/C calcium binding site and thereby alter the performance of the α-amylase.

216. Bott claim 2, which depends from claim 1, and Bott claim 3, which depends from claim 2, further limit the α-amylases that are to be modified by requiring that they are produced by the genus Bacillus, and by three species of Bacillus, respectively.

217. Bott claim 6 reads:

> The α-amylase according to claim 1, wherein said α-amylase further comprises a substitution or deletion at one or more residues equivalent to M15, V128, H133, W138, W138, N188, A209 and/or M197 in *Bacillus licheniformis*."

(BX 2003 at col. 28, ll. 60-63.)

218. Bott claim 7 reads:

> The α-amylase according to claim 1 which is modified by substituting an amino acid residue at a position corresponding to one or more of G301, H405, H406 and/or K436 in *Bacillus licheniformis*.

(BX 2003 at col. 28, ll. 64-67.)

219. Independent Bott claim 18 tracks the language of Bott claim 1, but contains the language, "wherein said α-amylase is modified . . . by substituting an amino acid residues at a position corresponding to H406 in *Bacillus licheniformis*."

(BX 2003 at col. 30, ll. 23-31.)

220. More specifically, Svendsen argues that Bott claims 1-3, 7, and 18 are anticipated by the disclosure in *Declerck 1990* of α-amylases from BLA that is modified at H406 by substitution with alanine (A, ala), glutamic acid (E, glu), phenylalanine (F, phe), proline (P, pro), leucine (L, leu), serine (S, ser), glutamine (Q, gln), tyrosine (T, tyr), and glycine (G, gly). (Paper 34 at 10-12, citing SX 1008 at 15484, Tables I and II; and the Borchert declaration, SX 1021 at ¶ 90.)

221. Borchert testifies that *Declerck 1990* describes a BLA α-amylase in which glutamine (E, gln) is substituted for the H406 histidine (H, his) residue, resulting in a residual amylase activity of 39, compared to a value of 28 for the native H406 α-amylase. (SX 1021 at 26, ¶ 91.)

222. Svendsen concedes that *Declerck 1990* does not describe effects on calcium binding, but urges that the discovery of a new property does not make the old product patentable. (Paper 34 at 12.)

223. Svendsen argues further that Bott claim 6, which requires further substitution at another residue, including H133, is anticipated by *Declerck 1990* in the disclosure of H133, H406 double mutants. (Paper 34 at 5, ¶ 18 and at 12-13, citing SX 1008 at 15484, Tables 1 and II; and SX 1021, ¶ 92.)

224. Bott responds that neither Svendsen nor Borchert demonstrated that any of the α-amylase mutants, including the H406 mutants, had altered calcium binding properties. (Paper 84 at 12.)

225. Bott responds further that Borchert acknowledged that *Declerck 1990* disclosed that there was no difference in the performance of the enzyme due to the substitution at H406. (Paper 84 at 5, ¶ 18 (citing Borchert testimony, BX 2055 at 65-67, and at 13.)

226. Regarding the conclusions of *Declerck 1990* about whether differences in activity were observed, Borchert testified:

> The authors themselves do note that there are different values on residual activity. But based on, I guess, the experimental error in the experiment, they say that "between 20 and 40 percent residual activity were considered as being not significantly different from those obtained with the wild-type enzyme."
>
> And if one accepts this as being the limits for how to interpret the data, I can't really – I don't have the basis to say that the authors' way of looking at the data is wrong. So I would have to better accept that this is the case.

(BX 2055 at 66, ll. 7-20.)

227. Bott concludes that anticipation has not been proved. (Paper 84 at 13.)

228. Svendsen replies that H406 was characterized by

Declerck 1990 as "neutral" with respect to thermostability only, and that a significant alteration of activity is shown in Table I of that reference. (Svendsen reply 7, Paper 99 at 5-6.)

229. Svendsen also urges that H406 is one of the calcium binding ligand residues, i.e., that it forms a chemical bond with the calcium ion, and that changing it must affect the calcium binding site.

discussion

"The first step of an anticipation analysis is claim construction." *Helifix, Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1346, 54 USPQ2d 1299, 1303 (Fed. Cir. 2000). "A claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) (citation omitted).

We have already provided an extensive analysis of the construction of Bott claim 1 in the context of the motions for lack of enablement. It suffices for the analysis of the present prior art motion to emphasize that the Bott claims require the substitution of at least one of the recited residues by a different residue, and that they are not limited to such substitutions. As shown by Bott claims 6 and 7, other residues may be substituted or even deleted. We have already held that

the alteration of the characteristics of the calcium binding site and alteration of the performance of the α-amylase are merely recitations of properties of the resulting compound. When dealing with claims to chemical compounds, it is critical to keep in mind that "[f]rom the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

Declerck 1990 discloses numerous modified BLA in which H406 has been substituted by other amino acids, alanine (A, ala), glutamic acid (E, glu), phenylalanine (F, phe), proline (P, pro), leucine (L, leu), serine (S, ser), glutamine (Q, gln), tyrosine (T, tyr), and glycine (G, gly). (SX 1008 at 15484, Tables I and II.) Declerck also discloses double mutants of BLA, in which both H406 and one of sites H133, H246, and H293 are changed to the indicated other amino acid residues. (*Id.*) Declerck testified that "[t]he resulting variant α-amylases were shown to retain 'alpha-amylase activity,' as measured by enzyme activity in Table II.") Bott describes H406 as one of the ligand residues of the A/C calcium binding site. (BX 2003 at col. 6, ll.58-67.) Regarding substitutions at the A/C calcium binding site, Declerck testified:

> A (by Declerck): . . . for this purpose [to increase the stability of the calcium binding site] you don't want to target the calcium binding site directly.
>
> Q Why not?
>
> A because – because you probably are going to destroy the binding. I mean, you're not going to do better than nature there. I mean, I don't believe so.

(BX 2053 at 150, l. 21 through 151, l. 6.) Thus, although *Declerck 1990* does not address whether the characteristics of the A/C calcium binding site are modified by the substitutions at H406, it is reasonable to presume that replacement of a ligand bonded to calcium in BLA would affect calcium bonding at that site.

It is irrelevant whether or not *Declerck 1990* describes the effects of substitution at H406 on calcium binding characteristics of BLA. The key point is, as Svendsen argues, that the discovery of a new property does not make a known substance patentable. (Paper 34 at 12.) *Declerck 1990* states:

> It was important to assess two points before interpreting the values obtained for the variants. . . . The range of responses observed with these controls reflects variations due both to the test procedure and the suppression method. Although this fluctuation is limited, it obviously prevents detection of minor modifications of enzyme parameters.
>
> **Due to this limitation**, for interpreting the data in Table II residual activity values ranging from 20 to 40% **were considered** as being not significantly

> different from those obtained with the wild-type enzymes. Within these detection limits, we concluded that most of the amylase variants exhibited a thermoinactivation similar to the wild-type amylase. Substitution of either one or two histidine residues at position His^{35}, His^{247}, His^{293}, His^{406}, or His^{450} had no detectable effect on the thermostability of the variants **in the conditions used here.**

(BX 2018 at 15485, col. 2, last two paragraphs, emphasis added.) Clearly, *Declerck 1990* does not teach that there were no effects on thermostability, but that the conditions of testing were such that the differences, if any, could not be reliably determined. We find that Svendsen established a *prima facie* case that Bott claims 1-3, 7, and 18 are anticipated by *Declerck 1990*. Bott did not come forward with probative evidence to the contrary, i.e., to show that, in spite of the change of a residue directly bonded to calcium, the characteristics of the calcium binding at that site were not affected.

Accordingly, the portions of Svendsen preliminary motion 7 that rely on *Declerck 1990* are GRANTED.

Holm

230. Svensen urges that the disclosure by *Holm* (BX 2006) of *B. stearothermophilus* α-amylases containing substitutions at D343, I428, or K436, which are said to correspond to BLA residues Q340, I428, and K436, and which are said to result in altered enzyme activity, anticipate Bott claims 1-3, 7, 14, 22, and 25.

(Paper 34 at 15-16.)

231. Svendsen concedes that *Holm* does not describe that these modifications affect the calcium binding property of the modified α-amylases, but urges that the discovery of a new property does not render an old product patentable. (Paper 34 at 16.)

232. Bott responds that Svendsen has failed to carry its burden of showing that the modification in *Holm*, which Bott characterizes as addressing a calcium binding site associated with the A and B domains. (Paper 84 at 14.)

233. Bott objects further that a modified α-amylase having total loss of amylase activity is not within the scope of its claims. (Paper 84 at 14.)

discussion

We have held, in accord with Bott's express definition ("'α-amylase' means any enzymatic activity which cleaves or hydrolyzes the α(1-4) glycosidic bond, e.g., that in starch, amylopectin or amylose polymers" (BX 2003 at col. 5, ll. 39-41), that Bott's claims only cover active modified α-amylases. A polypeptide similar to α-amylase in composition and structure that does not break down starch has, on the present record, no disclosed or apparent utility, and is therefore not an "α-amylase" within the meaning of the claims. The compounds

taught by *Holm are inactive*. Therefore, Svendsen's motion is DENIED as to the anticipation of Bott claims 1-3, 7, 14, 22, and 25 by *Holm*, notwithstanding that the substitutional mutants taught by *Holm* meet the structural limitation recited by Bott's claims.

WO 94/18,314

234. Svendsen urges that Bott claims 4 and 5, which are drawn to a detergent and a starch liquefaction composition, respective, would have been obvious over the combined teachings of either *Declerck 1990* or *Holm*, described *supra*, and WO94/18,314[35] ("WO 314"; SX 1017), which is said to suggest the use of α-amylases, and variants thereof in starch processing and detergent compositions. (Paper 34 at 19-20.)

235. Bott does not deny that WO 314 teaches the use of α-amylases and similar enzymes in detergents and starch liquifaction compositions, but argues that it does not cure the deficiencies of the primary references. (Paper 84 at 15.)

discussion

WO 314 does not cure any of the deficiencies of *Holm*. Accordingly, the portions of Svendsen preliminary motion 7 that rely on the combined teachings of *Holm* and the WO 314 reference

[35] WO 94/18,314, published 18 August 1994; applicant Genencor Int'l, Inc.; first inventor, Richard L. Antrim; "Oxidatively stable alpha-amylase."

are DENIED.

However, we have found that *Declerck 1990* anticipates Bott claims 1-7, 14, 18, 22, and 25. *Declerck 1990* notes that, "[f]or its remarkable activity and stability at extreme temperature and pH, the amylase secreted by *B. lichiformis* is the liquefying enzyme most widely used in the industrial processes of starch hydrolysis." BX 2018 at 15481, col. 2, 2d full paragraph.) Even without the additional teachings of WO 314, one of ordinary skill in the art would have been motivated to use the modified α-amylases taught by *Declerck 1990* in detergent and starch liquefaction compositions. Accordingly, we hold that Svendsen claims 4 and 5 would have been obvious over the combined teachings of *Declerck 1990* and WO 314.

Svendsen preliminary motion 7 is GRANTED as to claims 1-7, and 18, but DENIED as to claims 14, 22, and 25.

Motions to add claims

Bott preliminary motion 7

236. Bott seeks to add reissue application/control number 10/927,657 to this interference with the aim of correcting a number of typographical irregularities or "errors" in its patent claims, and to add certain further claims. (Paper 38 at 2-5.)

237. Bott's reissue application has not been examined as of

the date of this decision.

Generally, the Board will not add to an interference an application that has not been examined and determined to be patentable by a primary examiner. However, in view of our determination that none of Bott's patented claims remain patentable to Bott, we exercise our discretion to consider whether the addition of the reissue application would be likely to advance the determination of priority in this interference.[36]

238. Bott proposes to amend its patented claims by adding the conjunction "and," and by correcting various typographical errors. (BX 2042 at 2-7.)

None of these changes affect the way we have read the corresponding claims in Bott's involved 385 patent.

239. Bott proposes to add claims 29-35, which variously depend from independent claims 13, 17, 18, 26, and 27. (BX 2042 at 7-8.)

240. Independent claims 13, 17, 18, 26, and 27, are substantially identical to claim 1, except that they each recite a different single amino acid residue that must be substituted,

---

[36] Our considerations here do not bind the Director or the examiner acting on the Director's behalf, in the determination of whether the terms of 35 U.S.C. § 251 have been met, such that the reissue application is proper. Moreover, our use of terms such as "error" in this section is a descriptive convenience, and is not intended to imply any conclusion as to the legal characterization of the alleged errors.

selected from the list of such residues recited in claim 1. (BX 2042 at 3, 4, 5, 6, and 7.)

241. Proposed dependent claims 29-35 each recite one or two amino acids that are to be substituted for the particular residue recited in the corresponding independent claim. (BX 2042 at 7 and 8.)

242. None of the proposed dependent claims further limit the α-amylases that may be selected for alteration.

None of the amended claims, and none of the proposed additional claims, are free from the lack of enablement we have held prevents Bott from retaining a patent to the original claims. More specifically, our holding that undue experimentation would have been required to determine which α-amylases have residues that "correspond" to the recited residues, and which residues correspond to the recited residues of BLA (SEQ ID NO:2), due to the necessity of obtaining additional crystals suitable for the determination of x-ray crystal structures, applies to these claims as well. Moreover, our holding that undue experimentation would have been required to develop and conduct assays to determine whether the modified A/C calcium binding site and altered performance limitations were met with the 385 patent claims applies to all of the claims proposed for the reissue application. Thus, on the present

record, none of the claims in the Bott reissue application are patentable to Bott.

Accordingly, Bott preliminary motion 7 is DENIED.

Svendsen preliminary motion 11, to add claims to Bott's reissue application, is contingent on the grant of Bott preliminary motion 7, and is therefore DISMISSED.

Svendsen preliminary motion 13

243. Svendsen preliminary motion 13 replaces Svendsen preliminary motion 10.

244. Svendsen seeks to add claims 214-218 to its specification in response to Bott preliminary motions 2-5. (Paper 128 at 1.)

245. Bott preliminary motion 3 has been granted in sufficient part that it is appropriate to consider Svendsen's responsive motion.

246. Proposed claim 214 reads:

> A variant of a parent *Bacillus* alpha-amylase, wherein said parent has the amino acid sequence shown in SEQ ID NO:2, 4, or 6, said variant having an amino acid sequence which differs from the amino acid sequence of said parent, wherein the difference between said variant and said parent consists of a different amino acid residue in said variant than in said parent at one or more positions selected from the group consisting of the positions which correspond to amino acid residues Q298, G299, G301, L307, F343, F403, H405, D407, L427, D430, and G475 in *Bacillus licheniformis* alpha-amylase (SEQ ID NO:2); wherein said variant has alpha-amylase

activity.

247. Proposed claims 215-218 read:

> 215. An alpha-amylase that is a variant of a *Bacillus licheniformis* alpha-amylase comprising SEQ ID NO:2, wherein Q298 is replaced with glutamic acid (E).
>
> 216. An alpha-amylase that is a variant of a *Bacillus licheniformis* alpha-amylase comprising SEQ ID NO:2, wherein F343 is replaced with tryptophan (W).
>
> 217. An alpha-amylase that is a variant of a *Bacillus licheniformis* alpha-amylase comprising SEQ ID NO:2, wherein L427 is replaced with phenylalanine (F).
>
> 218. An alpha-amylase that is a variant of a *Bacillus licheniformis* alpha-amylase comprising SEQ ID NO:2, wherein L427 is replaced with tryptophan (W).

248. For all of these claims, Svendsen points to its specification (SX 1007) at 4, ll. 21-23 and at 5, ll. 7-11, for support of recitation of a variant of BLA comprising SEQ ID NO:2, 4, or 6. (Paper 128 at 8 and 10.)

249. With regard to claim 214, Svendsen identifies support for the list of amino acid residues recited in claim 214 at (SX 1007, p, ll) (22, 22-30), (23, 12-15), (24, 15-18), (32, 22-30), and (39, 18-20). (Paper 128 at 8.)

250. Regarding claim 215, Svendsen cites (4, 15) and (5, 7-11) as support for the replacement of Q298 with glutamic acid, E. (Paper 128 at 10.)

251. Regarding claim 216, Svendsen cites (24, 15) and (32, 21) as support for the replacement of F343 with

tryptophan, W. (Paper 128 at 10.)

252. Regarding claim 217, Svendsen cites (32, 22-25) and (32, 30) as support for the replacement of L427 with phenylalanine, F. (Paper 128 at 10.)

253. Regarding claim 218, Svendsen cites (32, 22-25) and (32, 30) as support for the replacement of L427 with tryptophan, W. (Paper 128 at 10.)

254. Bott, in Opposition 10 (Bott was not permitted to file an Opposition to Svendsen preliminary motion 13 (Paper 121 at 13)), urges that the claims are unpatentable over prior art. (Paper 87 at 11.)

255. Bott's first theory appears to be that all of the claims are directed to the same invention because the residues are all identified by being within 10 Å of the A/C binding site. Bott concludes that "[a] reference that meets one of these, will meet the others, absent an explanation as to why not."

256. Bott's second theory – to the extent that it is distinct from the first theory – appears to be that the selection of one residue is obvious over the selection of any other residue, given the exploration in the prior art of "the consequences of altering a large number of residues [list]." (Paper 87 at 11-12.)

257. Bott urges further that the Svendsen claims, which do

not recite any function for the claimed modified α-amylases, fail for lack of substantial utility. (Paper 87 at 12-13.)

discussion

Proposed claims 214-218 are drawn to subject matter within the scope of, e.g., Svendsen claim 113 and Bott claim 1. As Svendsen points out (Paper 128 at 13, 15), claims 214-218 are limited to modifications of polypeptides specified by SEQ ID NOs. Accordingly, the issue of enablement due to the necessity of obtaining additional X-ray crystal structures is avoided, both for the selection of potential α-amylases for modification, and for determination of which residues correspond to the recited residues of BLA, SEQ ID NO:2. There appears to be no dispute that the SEQ ID NO:2, 4, and 6 are adequately correlated in the prior art of record that "corresponding" residues would have been identifiable by those skilled in the art. None of the claims recite the functional characterizations that we have held would have required undue experimentation to determine. Moreover, as Svendsen notes (Paper 128 at 14), the substitutions taught by the prior art are not recited in any of the claims.

Bott's arguments that the remaining residues recited by Svendsen are obvious are without merit. A proof that a claim is obvious requires a proof that each of the limitations of the claim were known and that the combination of limitations would

have been suggested by something in the prior art. Bott has neither directed our attention to such teachings in the prior art nor related them to the particular limitations of the present claims.

Bott's argument that the claimed subject matter lacks utility fails. Svendsen's specification states that the purpose of the invention is to provide variants of native α-amylases, "which variant has α-amylase activity and at least one altered property as compared to said parent α-amylase." (SX 1007 at 3, ll. 2-3.) This statement is not an assertion of incredible utility, as the same function (starch degradation) is asserted for the modified product as for the "parent" product. Moreover, Bott has failed to come forward with specific reasons why the operability of the claimed compounds is in doubt. While certain embodiments within the scope of the claims may not work, that issue sounds in enablement, and there is no evidence that that determination would involve undue experimentation.

Finally, the residues recited for substitution in these claims are disclosed in Svendsen's specification at the places cited by Svendsen it its argument. (See, e.g., SX 1007 at 24, list of residues.) Bott not argued that the claimed subject matter is not described.

In conclusion, Svendsen preliminary motion 13 is GRANTED.

Reformation of the Count

As a result of our determinations on preliminary motions, Bott no longer has any patentable claims. Svendsen has only claims 192, which defines an alternative of Count 2, and 214-218, which correspond to Count 2. Count 2, which now includes claims we held to be unpatentable, is no longer a proper vehicle in which to contest priority.

Even though Bott no longer has any patentable claims, it may be that Bott can prove priority. Because the subject matter of Svendsen's remaining claims is within the scope of the original Count, we deem it appropriate that the Count be reformulated according to all of Svendsen's claims. This interference will be redeclared according to Count 3 in a separate Order mailed on the same date as this Decision.

Motion for benefit

258. In Svendsen preliminary motion 14, Svendsen seeks to be accorded the benefit for priority of its parent US, PCT, and Dutch priority applications with respect to Count 2. (Paper 132 at 1.)

259. Claim 192 defines an alternative of the Count in this interference. (Paper 121 at 12 and Paper 154.)

260. Svendsen identifies text in DK 0128/95 (EX 1001) at 20, l. 14, to 21, l. 15, as disclosing the exact substitution recited

in claim 192. (Paper 132 at 18.)

261. Svendsen identifies text in DK 1192/95 (EX 1002) at 27, l. 20, to 28, l. 21, as disclosing the exact substitution recited in claim 192. (Paper 132 at 18-19.)

262. Svendsen identifies text in DK 1256/95 (EX 1003) at 27, l. 20, to 28, l. 21, as disclosing the exact substitution recited in claim 192. (Paper 132 at 19.)

263. Svendsen identifies text in PCT/DK96/00057 (SX 1004) at 28, l. 11, to 29, l. 12, as disclosing the exact substitution recited in claim 192. (Paper 132 at 19.)

264. Svendsen identifies text in US application 08/600,908 (SX 1005) at 22, ll. 8-31, as disclosing the exact substitution recited in claim 192. (Paper 132 at 20.)

265. Svendsen identifies text in US application 08/683,838 (SX 1006) at 22, l. 21, to 23, l. 15, as disclosing the exact substitution recited in claim 192. (Paper 132 at 20.)

266. Bott argues that there is no showing of utility for the polypeptide of claim 192 in the Dutch priority documents, and that these documents must fail as constructive reductions to practice. (Paper 142 at 13-16.)

267. Bott does not deny that the priority documents contain the text relating to the claimed subject matter at the places indicated by Svendsen.

discussion

Review of the priority documents shows that Svendsen's representations are accurate. Bott does not contest that the particular substitutions are disclosed at the places indicated. Bott's arguments regarding the absence of utility, and therefore a failure of constructive reduction to practice, are without merit. Each of the applications discusses the substitution of a loop of one kind of α-amylase into another α-amylase as a way of introducing certain properties, e.g., selectivity, of the first α-amylase into the second. Indeed, the discussions of loop modifications in these documents is substantially the same as the discussion in Svendsen's involved 563 application, which we considered at length, *supra*. The utility disclosed by Svendsen for the polypeptide of claim 192 is the same as that of the "parent" α-amylase, to digest starch. Bott's arguments do not show that the claimed polypeptide is not useful in this way.

Svendsen preliminary motion 14 is GRANTED in that Svendsen is accorded the benefit for priority of DK 0128/95 (EX 1001), DK 1192/95 (EX 1002), DK 1256/95 (EX 1003), PCT/DK96/00057 (SX 1004), and applications 08/600,908 (SX 1005) and 08/683,838 (SX 1006).

Miscellaneous motions

268. Bott filed a motion to suppress the declaration of Osnat Herzberg (SX 1046). (Paper 126.)

As we have not relied on the testimony of Dr. Herzberg, we DISMISS Bott's motion as moot.

269. Svendsen seeks leave to file a Certificate of Correction in Patent 6,022,724 ("724 patent") to correct an alleged mistake by the USPTO in which Svendsen application 08/600,908 is incorrectly stated to have been filed under 35 U.S.C. § 371, rather than as a continuation under 37 CFR § 120. (Paper 35 at 2.)

270. Bott has not opposed this motion.

271. The 724 patent is not involved in this interference.

This motion is DISMISSED without prejudice to Svendsen taking what ever action it deems proper regarding the 724 patent.

IV. Order

In view of the findings of fact and conclusions of law set out above, it is:

ORDERED that Bott preliminary motion 2 is GRANTED- as to Svendsen claim 204, but is otherwise DENIED.

FURTHER ORDERED that Bott preliminary motion 3 is GRANTED as to Svendsen claims 77-81, 84-88, 90-92, 97, 113-118,

120, 194-196, 198-201, 203, 204, 206, and 208; but DENIED as to Svendsen claim 192.

FURTHER ORDERED that Bott preliminary motion 4 is DENIED.

FURTHER ORDERED that Bott preliminary motion 5 is DENIED.

FURTHER ORDERED that Bott preliminary motion 6 is DENIED.

FURTHER ORDERED that Bott preliminary motion 7 is DENIED.

FURTHER ORDERED that Bott preliminary motion 8 is DISMISSED.

FURTHER ORDERED that Bott's motion to suppress testimony by Herzberg is DISMISSED.

FURTHER ORDERED that Svendsen preliminary motion 4 is DENIED.

FURTHER ORDERED that Svendsen preliminary motion 5 is GRANTED.

FURTHER ORDERED that Svendsen preliminary motion 6 is DENIED.

FURTHER ORDERED that Svendsen preliminary motion 7 is GRANTED as to Bott claims 1-7 and 18, but DENIED as to Bott claims 14, 22, and 25.

FURTHER ORDERED that Svendsen preliminary motion 11 is DISMISSED.

FURTHER ORDERED that Svendsen preliminary motion 12 is DISMISSED.

FURTHER ORDERED that Svendsen preliminary motion 13 is GRANTED.

FURTHER ORDERED that Svendsen preliminary motion 14 is GRANTED.

FURTHER ORDERED that Svendsen's motion to suppress evidence is DISMISSED.

FURTHER ORDERED that RICHARD R. BOTT and ANDREW SHAW are not entitled to a patent containing Bott claims 1 through 28.

FURTHER ORDERED that ALLAN SVENDSEN, HENRIK BISGARD-FRANTZEN, and TORBEN BORCHERT are not entitled to a patent containing Svendsen claims 77-81, 84-88, 90-92, 97, 113-118, 120, 193, 194-196, 197, 198-201, 203, 204, 205, 206, 208, and 209-213.

FURTHER ORDERED that proposed claims 214-218 are added to Svendsen application 09/327,563.

FURTHER ORDERED that the attention of the parties is directed to the Redeclaration of this interference according to Count 3, set out in Paper 154, which is mailed on the same date as this Decision.

FURTHER ORDERED that if there is a settlement, the

attentions of the parties are directed to 35 U.S.C. § 135(c) and 37 CFR § 41.205.

FURTHER ORDERED that this paper be given an appropriate number and placed in the files of U.S. Patent 5,763,385, Bott Reissue Application 10/927,657, and Svendsen application 09/327,563.

Alexandria, VA
26 September 2005

cc: via overnight mail:

Counsel for Bott:

Samuel B. Abrams, Esq.
JONES DAY
222 East 41st Street
New York, NY 10017-6702

Phone: 212-326-3875
Fax: 212-755-7306

Counsel for Svendsen:

John T. Callahan, Esq.
2100 Pennsylvania Ave., NW
Suite 800
Washington, DC 20037

Phone: 202-293-7060
Fax: 202-293-7860

The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper ~~154~~ 30

Filed by: Administrative Patent Judge James T. Moore
Mail Stop Interference
P.O. Box 1450
Alexandria, VA 22313-1450
Tel: 571-272-9797
Fax: 571-273-0042

Filed
26 September 2005

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge James T. Moore)

RICHARD R. **BOTT**
and ANDREW SHAW,

Junior Party[1],
(Patent 5,763,385),

v.

ALLAN **SVENDSEN**,
HENRIK BISGARD-FRANTZEN, and TORBEN BORCHERT,

Senior Party[2],
(Application 09/327,563).

MAILED

SEP 26 2005

PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Patent Interference No. 105,206

ORDER – REDECLARATION – BD.R. 203(C)

Count 3

1. In view of the Decision on Interlocutory Motions (Paper 153), it is

[1] The real party in interest is identified as Genencor Int'l, Inc.

[2] The real party in interest is identified as Novozymes A/S, of Denmark.

ORDERED that this interference is redeclared according to Count 3:

> A composition of matter in accordance with any one of claims 192, 214, 215, 216, 217, or 218 of Svendsen application 09/327,563.

2. The claims of the parties are:

Bott: none

Svendsen: 192, 214-218.

3. The claims of the parties that correspond to Count 3 and therefore are involved in the interference are:

Bott: none

Svendsen: 192, 214-218.

4. The claims of the parties that do not correspond to Count 3 and therefore are **not** involved in the interference are:

Bott: none

Svendsen: none.

5. Svendsen is accorded the benefit for priority of the following applications:

08/683,838 (SX 1006), filed 18 July 1996

08/600,908 (SX 1005), filed 13 February 1996

PCT/DK96/00057 (SX 1004), filed 5 February 1996

Denmark 0128/95, filed 3 February 1995 (SX 1001)

Denmark 1192/95, filed 23 October 1995 (SX 1002)

Denmark 1256/95, filed 10 November 1995 (SX 1003).

Standing Order

6. FURTHER ORDERED that the attention of the parties is further drawn to the **Standing Order** attached to this Order, which shall govern the further conduct of this proceeding.

Conference Call

7. FURTHER ORDERED that a conference call is scheduled for **1:00 p.m.** on **6 OCTOBER 2005** to discuss the priority phase of this interference. The call will be initiated by the Board.

Priority Schedule

8. FURTHER ORDERED that an Order setting a schedule for the priority phase of this interference will be issued in due course.

9. FURTHER ORDERED that if there is a settlement, the attentions of the parties are directed to 35 U.S.C. § 135(c) and 37 CFR § 41.205.

Alexandria, VA
26 September 2005

cc: via overnight mail:

Counsel for Bott:

Samuel B. Abrams, Esq.
JONES DAY
222 East 41st Street
New York, NY 10017-6702

Phone: 212-326-3875
Fax: 212-755-7306

Counsel for Svendsen:

John T. Callahan, Esq.
SUGHRUE MION, PLLC
2100 Pennsylvania Ave., NW
Suite 800
Washington, DC 20037

Phone: 202-293-7060
Fax: 202-293-7860